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(71) Applicant *(for all designated States except US)*: BRITISH TECHNOLOGY GROUP LTD. [GB/GB]; 101 Newington Causeway, London SE1 6BU (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: STRATFORD, Ian, James [GB/GB]; Bretton Cottage, Sir William Hill Road, Bretton, Eyam, Derbyshire S30 1QD (GB). NAYLOR, Matthew, Alexander [GB/GB]; 16 The Firs, The Laurels, Flamstead, Flamstead End, West Cheshunt, Hertfordshire EN7 6UD (GB). JAFFAR, Mohammed [GB/GB]; 51 Shelley Close, Abingdon, Oxon OX14 1PP (GB). ADAMS, Gerald, Edward [GB/GB]; 59 Ladder Hill, Wheatley, Oxford OX33 1HY (GB).

(74) Agent: DOLAN, Anthony, Patrick; British Technology Group Ltd., Patents Dept., 101 Newington Causeway, London SE1 6BU (GB).

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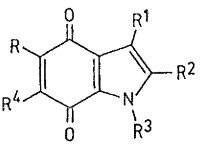
(54) Title: INDOLOQUINONE DERIVATIVES AS BIOREDUCTIVE AGENTS

(57) Abstract

Use of a compound of general formula (I) or salt thereof wherein R and R^4 are independently selected from hydrogen, halogen and C_{1-6} alkyl or haloalkyl, C_{2-5} alkenyl or haloalkenyl, C_{1-6} alkoxy, phenoxy, C_{1-6} alkylthio, phenylthio, primary and secondary amino or hydroxy groups and R^3 is hydrogen, hydroxy, a C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy or haloalkoxy group is provided for the manufacture of a medicament for the treatment of neoplasms, particularly solid cancerous tumours characterised in that R^1 is selected from a C_{1-6} alkyl or haloalkyl group, $-CO_2R^5$ where R^5 is hydrogen or a C_{1-6} alkyl or haloalkyl group, or a group $-CH_2-X$ where X is selected from groups of formula $-S-R^6$, $-O-R^6$, and (a) where R^6 is a hydrogen or a leaving group, the acid HR^6 of which has a pKa of 10 or less and R^7 and R^8 are the same or different and are selected from C_{1-6} alkyl or haloalkyl or together with the interjacent nitrogen form a heterocyclic ring of 5 to 7 atoms optionally substituted by C_{1-4} alkyl or haloalkyl and R^2 is selected from hydrogen, C_{1-4} alkyl and haloalkyl or groups $-(CH_2)_nCHR^9R^{10}$ of more than four carbon atoms where n is an integer of 0 to 2 and R^9 and R^{10} are independently selected from a C_{1-4} alkyl or haloalkyl group, or R^9 and R^{10} together with the interjacent carbon atom form a C_{3-7} cycloalkyl or cycloalkenyl ring optionally substituted with one or more C_{1-4} alkyl or haloalkyl, or C_{2-4} alkenyl or haloalkenyl groups.



(I)

(a)

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INDOLOQUINONE DERIVATIVES AS BIOREDUCTIVE AGENTS

The present invention relates to the use of a group of indoloquinones as therapeutic agents, particularly as bioreductively activated anti-tumour agents, to novel members of this group and compositions containing them and to methods of using these to treat tumours.

Fused cyclopropamitosenes and closely related indoloquinones have recently been evaluated as novel bioreductive anticancer agents (references 1-3 below). These compounds were originally designed as analogues of the archetypal quinone bioreductive alkylating agent mitomycin C (Figure 1 herein; MMC, compound **1**) having much reduced electophilicity at C-1 due to the inertness of the 1,2-cyclopropane compared to the aziridine in MMC. Certain indoloquinones (e.g. Figure 1; compound **2**) in this series have been found to be highly potent cytotoxins as compared with MMC and in some cases have substantially higher hypoxic cytotoxicity ratios (HCR) (see references 2-3). The cyclopropamitosenes have been found to be more rapidly reduced by DT-diaphorase, an important activator of mitosenes, compared to MMC, but this could not explain fully the higher potency of the compounds compared to the current lead clinical agent of this type EO9 (**3**), which is reduced two orders of magnitude more rapidly than compound **2** by DT-diaphorase (see WO 87/06227 ≡ US 5097257).

The presence of particular groups as the 5-substituent, in particular aziridines and substituted aziridines, and as the leaving group on the 3-methylene substituent was therefore identified as an important feature, both in terms of oxic and hypoxic potency and rate of reduction, i.e. ability to act as substrates for reductase enzymes. This does not vary greatly among 5-aziridine and 5-methoxy drivatives (see references 2 and 6 below), but it should be noted that the relative rates of reduction of this type of compound by one-electron reductases, which will be important under hypoxic conditions, is unknown, and there is very little data on one electron reduction potentials of mitosenes.

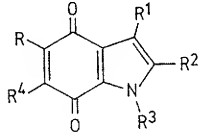
Ionic ring-opening of the fused cyclopropane is considered unlikely but radical ring opening of the cyclopropane to give a reactive H-atom abstractor has been suggested as a possible explanation for hypoxic potency in particular. There has however been no direct evidence for this mechanism.

The present inventors have now designed and synthesized analogues of compound **2** wherein *inter alia* (i) cyclopropane rings are included not fused to the indoloquinone ring system, (ii) lower alkyl eg. isopropyl analogues of these that are structurally very closely related to **2** but unable to undergo radical ring-opening reactions and (iii) analogues containing no substituent, ie. where R^2 is hydrogen. These derivatives have been designed as closer analogues of EO9 with the aim of targeting and exploiting DT-diaphorase activity. Particularly desirable is the optimization of hypoxic-cytotoxicity by such modifications and this novel series of compounds offers many compounds of relatively high HCR.

Some of the compounds used by the invention are disclosed in US patents US 3226397, US 3226398, US 3226399, US 3265698, US 3267117 and US 3226385; all corresponding to the single UK patent application GB 1087325. The UK documents lists three hundred and fifteen examples of which twenty seven are specified as having anti-microbial activity.

The compounds for the use of the present invention form a selection from the general formula of GB 1087325 and are those of the general class referred to in US 5097257 but distinguished therefrom by, inter alia, particular groups at R^1 and R^2 of the formula I below. The formula I, and particularly preferred members of that formula such as those of formula II, offer compounds with advantages of selective hypoxic and anoxic potency.

Thus in a first aspect of the present invention there is provided the use of a compound of general formula I



or a salt thereof

wherein

R and R^4 are independently selected from hydrogen, halogen and C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl, C_{1-6} alkoxy, phenoxy, C_{1-6} alkylthio, phenylthio, primary and secondary amino or hydroxy groups and

R^3 is hydrogen, hydroxy, a C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy or haloalkoxy group for the manufacture of a medicament for the treatment of neoplasms, particularly tumours and more particularly cancer tumours,

characterised in that

R^1 is selected from a C_{1-6} alkyl or haloalkyl group, $-CO_2R^5$, where R^5 is hydrogen or a C_{1-6} alkyl or haloalkyl group, or a group $-CH_2-X$, where X is selected from groups of formula $-S-R^6$, $-O-R^6$ and $-N<^{R7}_{R8}$ where R^6 is hydrogen or a leaving group the acid HR^6 of which has a pKa of 10 or less and R^7 and R^8 are the same or different and are selected from C_{1-6} alkyl or haloalkyl or together with the interjacent nitrogen form a heterocyclic ring of 5 to 7 atoms optionally substituted by a C_{1-4} alkyl group or haloalkyl

and

R^2 is selected from hydrogen, C_{1-4} alkyl and haloalkyl and $-(CH_2)_nCHR^9R^{10}$ of more than four carbons where n is an integer of 0 to 2 and R^9 and R^{10} are independently selected from a C_{1-4} alkyl or haloalkyl group, or R^9 and R^{10} together with the interjacent carbon atom form a C_{3-7} cycloalkyl or cycloalkenyl ring optionally substituted with one or more C_{1-4} alkyl or haloalkyl, or C_{2-4} alkenyl or haloalkenyl groups.

In a preferred use of the invention R is a C_{1-6} alkoxy, haloalkoxy, C_{2-4} alkenoxy or haloalkenoxy, phenoxy, C_{1-6} alkylthio, phenylthio, primary or secondary amino or hydroxy group; R^3 is preferably hydrogen, hydroxy, a C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy group and R^4 is preferably hydrogen, halogen or a C_{1-6} alkyl or haloalkyl, C_{2-4} alkenyl or haloalkenyl group.

Preferred salts are suitable for direct adminstration to patients and thus are pharmaceutically or 'physiologically' acceptable salts. Such salts may be made with a compound described above and a physiologically acceptable acid or, where the compound contains a suitable negatively chargeable group, base. Thus salts may be formed with various inorganic and organic acids. Examples of these acids are phosphonic, nitric,

sulphuric, hydrohalic, citric, oxalic, fumaric, maleic, lactic, succinic, malic, tartaric and methane sulphonic acids. Preferred halide salts are those of hydrochloric, hydrobromic or hydroiodic acid. Examples of bases are alkali metal hydroxides and quaternary ammonium hydroxides eg. 2-amino-2-hydroxymethyl propane-1,3-diol (Tris) salts.

R is preferably selected from C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{2-4} alkenoxy, C_{2-4} haloalkenoxy and aziridin-1-yl groups, the aziridin-1yl groups being optionally substituted with C_{1-4} alkyl, or C_{1-4} haloalkyl or C_{2-4} alkenyl or C_{2-4} haloalkenyl.

R^2 is preferably selected from C_{1-4} n-alkyl or -haloalkyl groups or groups of formula $-(CH_2)_nCHR^9R^{10}$, where n is an integer from 0 to 2, where R^9 and R^{10} are independently selected from C_{1-4} alkyl and C_{1-4} haloalkyl or together with the interjacent carbon atom form a C_{3-6} cycloalkyl or cycloalkenyl group optionally substituted with C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl or C_{2-4} haloalkenyl.

Preferably R^2 is a C_{1-4} n-, iso- or cyclo-alkyl group, particularly a methyl or cyclopropyl groups.

R^3 is more preferably selected from C_{1-4} alkyl or haloalkyl and C_{2-4} alkenyl and haloalkenyl groups.

R^4 is more preferably selected from hydrogen, C_{1-4} alkyl and haloalkyl groups and most preferably is hydrogen.

Particularly preferred compounds are those where R is aziridin-1-yl optionally substituted with C_{1-4} alkyl or C_{1-4} haloalkyl or where R is C_{1-4} alkoxy.

One group of preferred compounds are those where the group R^1 is selected from $-CH_2-O-R^6$ and $-CH_2-S-R^6$ where R^6 is hydrogen or where R^6 is an optionally substituted phenyl or benzyl group or a group -C(O)-R11 where R^{11} is an optionally substituted phenyl, benzyl or amino group; examples of such groups R^1 including alkoxy, aryloxycarbonyloxy, aryloxycarbonyloxy and carbamoyloyloxy. Optional substituents include halo, C_{1-6} alkyl or haloalkyl, nitro and sulpho groups. Conveniently R^1 is hydroxymethyl.

Still more preferred compounds are those wherein R^1 is a group $-CH_2X$ where X is $-N\begin{matrix}R^7\\R8\end{matrix}$ wherein R^7 and R^8, together with the interjacent nitrogen form a 5 to 7 membered

heterocyclic ring containing nitrogen and carbon with optional oxygen or sulphur members, e.g. piperazine, morpholine, thiomorpholine rings. More preferably the heterocyclic ring is a piperazinyl ring optionally substituted by one or more C_{1-4} alkyl or haloalkyl groups. It is particularly preferred that X is a 4-alkylpiperazin-1-yl group, eg. a 4-methylpiperazine group.

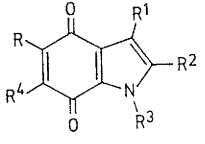
R^3 is most preferably a C_{1-4} alkyl group and R^4 is most preferably hydrogen.

Particularly preferred compounds include those where R is aziridin-1-yl optionally substituted with C_{1-4} alkyl, eg. 2-methylaziridin-1-yl, R^2 is cyclopropyl or isopropyl or C_{1-4} n-alkyl, R^3 is methyl and R^4 is hydrogen.

The most preferred compounds for the use of the invention are those which have a $C_{50}(Air)\mu M/C_{50}(N_2)\mu M$ ratio of 40 or more, still more preferably of 100 or more. No particular upper limit applies to preferred compounds as a relatively selective action against hypoxic or anoxic cells is desired. It is also preferred that the compounds have a hypoxic potency such that their $C_{50}(N_2)$ value is less than 10μM, more preferably less than 1μM and most preferably less than 0.01μM. Typically this is in the range 0.005 to 1 μM.

Most preferred compounds are described herein as compounds 21, 54 and 84 of the Examples described below; the numbers being in brackets at the end of the example title.

In a second aspect of the invention there are provided novel compounds falling within formula I above. Particular novel compounds of the invention are those of formula Ia below. Thus this second aspect of the present invention provides a novel compound of formula Ia



or a salt thereof

characterised in that

R is C_{1-4} alkoxy or haloalkoxy or aziridin-1-yl optionally substituted with one or more C_{1-4} alkyl or haloalkyl groups,

R^4 is hydrogen or a C_{1-4} alkyl or haloalkyl group,

R^3 is hydrogen, hydroxy, C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy or haloalkoxy,

R^1 is $-CO_2R^5$ where R^5 is a hydrogen or C_{1-6} alkyl or haloalkyl group, or is a group $-CH_2X$ where X is selected from $-S-R^6$, $-O-R^6$ and $-NR^7R^8$ where R^6 is hydrogen or a leaving group the acid HR^6 of which has a pKa of 10 or less and R^7 and R^8 are the same or different and are selected from C_{1-6} alkyl or haloalkyl or together with the interjacent nitrogen form a heterocyclic ring of 5 to 7 atoms optionally substituted by a C_{1-4} alkyl or haloalkyl group and

R^2 is hydrogen or a C_{1-4} alkyl group or a group $-(CH_2)_nCHR^9R^{10}$ of more than four carbons where n is an integer of 0 to 2 and R^9 and R^{10} are independently selected from C_{1-4} alkyl and haloalkyl or R9 and R10 together with the interjacent carbon atom form a C_{3-7} cycloalkyl or cycloalkenyl ring optionally substituted with one or more C_{1-4} alkyl or haloalkyl or C_{2-4} alkyl or haloalkyl groups;

with the provisos that

(i) when R is methoxy, R^1 is hydroxymethyl or a carbamate or C_{1-6} aliphatic ester thereof, R^4 is methyl or ethyl and R^3 is methyl, optionally 2-substituted ethyl, propyl or butyl, then R^2 is not hydrogen, methyl, fluoromethyl, chloromethyl or ethyl,

(ii) when R is methoxy, R^4 is hydrogen, R^1 is hydroxymethyl or the propylcarbamate thereof and R^3 is ethyl, then R^2 is not methyl,

(iii) when R is methoxy, R^2 is methyl, R^3 is ethyl and R^4 is methyl, then R^1 is not hydroxymethyl cyclohexylcarboxylate, benzoate, furanyl-2-carboxylate, 3-(2-dimethylaminoethyl)-piperazine-1-carboxylate, morphalinocarbamate, 4-(3-hydroxypropyl)-piperazinecarbamate or 4-(3-dimethylaminopropyl)-piperazinecarbamate,

and

(iv) when R is aziridinyl or ethoxy, R^1 is hydroxymethyl or a carbamate or C_{1-6} aliphatic ester thereof, R^4 is methyl or bromo and R^3 is ethyl, then R^2 is not methyl.

Preferred novel compounds of the invention are those where R^1 is a hydroxymethyl group or a group $-CH_2-X$ as defined above. Most preferred novel compounds are those where R is aziridin-1-yl or 2-alkyl-aziridin-1-yl, such as 2-methyl-aziridin-1-yl.

R^3 is preferably C_{1-4} alkyl or haloalkyl and R^2 is preferably n-C_{1-4} alkyl, isopropyl or C_{3-7} cycloalkyl. R^4 is preferably methyl or hydrogen, most preferably hydrogen.

A third aspect of the present invention provides a novel compound of the second aspect of the invention or a physiologically acceptable salt thereof for use as a therapeutic agent.

A preferred use as therapeutic agent as provided by this invention is for the treatment of tumour cells, and most preferably the use is that which adminsters the compound in treatment also comprising radiation treatment, e.g. with therapeutic radiation such as X-rays, γ-rays and electrons from an accelerator, e.g. linear accelerator. The use of the compound with radiation is particularly effective for achieving cytostasis and/or death of tumour cells, particularly of cancer cells. Most preferably the use is aimed at providing cytotoxicity of anoxic tumour cells, ie. those relatively poorly supplied with blood.

Particularly the use is aimed at providing cytotoxicity towards hypoxic and anoxic tumour cells which, at the time of treatment, exist at an oxygen tension of less than 7.6 mm Hg of O_2 (1%).

A fourth aspect of the present invention provides compositions comprising a novel compound of the second aspect of the invention or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier. Compositions will preferably be provided as discrete dosage units and packs thereof, e.g. in a form suitable for parenteral or oral adminstration. Other suitable dosage unit forms will occur to those skilled in the art.

A fifth aspect of the present invention provides a method of treating a human or animal body for the purposes of killing, and/or preventing growth of, tumour cells comprising administering a medicament manufactured with the compound of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, to the body in a dose sufficient to kill or prevent growth of some or all of the tumour cells.

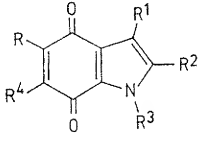
Preferred methods of the fifth aspect are for treating hypoxic and anoxic tumour cells, particularly cancer cells. It will be realised that the treatment will usually include killing of oxic cells, but that in preferred forms the ratio of such cells killed as compared with anoxic or hypoxic cells will be relatively low.

A still more preferred method of the fifth aspect comprises administering the medicament manufactured with the compound or salt of the first aspect to the body within a set period of treatment of the body with doses of radiation, the doses of radiation being sufficient to kill or prevent growth of some or all of any oxic tumour cells eg. those relatively well supplied with blood. This combination treatment allows targeted radiation to be used to damage and/or kill the oxic tumour cells while the systemically adminstered compound of the invention is used to damage or kill the hypoxic and anoxic cells selectively, thus causing reduced peripheral damage to healthy non-tumour cells.

The compounds of the present invention are of the indoloquinone class and as such will have application in treatment of tumours such as those vulnerable to mitomycins and the compounds disclosed in US 5079257. These include all solid tumour types, for example cervical, breast, pancreatic and prostatic adenocarcinoma, colon, bladder, gastro-intestinal cancers and melanomas. Such tumours may exist in an area of hypoxia and contain the reductive enzymes necessary to activate the agents for the use of this invention.

A sixth aspect of the invention provides novel compounds that have utility as intermediates for use in the preparation of a compound of the first aspect of the invention, these intermediates being novel compounds as described in the Figures 2 to 5 and the Examples 1 to 49.

Particularly preferred novel intermediates are those of formula II below



Formula II

wherein R is C_{1-4} alkoxy, R^1 is C_{1-4} alkoxycarbonyl and R^2, R^3 and R^4 are as for formula Ia. It will be realised that some of these compounds will also be compounds of the first aspect of the invention but, where these have an HCR of less than 40, and particularly have an HCR of less than 10, their main interest will be as intermediates for use in synthesis of the more preferred compounds. In this respect the 5-alkoxy compounds will usually have a less favourable efficacy and HCR ratio than the corresponding aziridinyl compounds and thus their prime use will be as intermediates. Preferred intermediates are those where R is methoxy, R^1 is methoxycarbonyl and R^3 is methyl.

A seventh aspect of the present invention provides a process for preparing compounds of formula Ia and II.

In a first preferred process of this aspect there is provided a process for preparing an optionally substituted aziridin-1-yl compound of formula II where R^1 is alkoxycarbonyl comprising reacting a corresponding 2-substituted-3-alkoxycarbonyl-5-alkoxy-1-alkyl-indole-4,7-dione with an optionally substituted aziridine.

In a second preferred process for preparing a compound of formula Ia where R^1 is a hydroxymethyl group a corresponding 2-substituted-3-alkoxycarbonyl-5-alkoxy-1-alkyl-indole-4,7-dione is reacted with an oxidising reagent, such as $Na_2S_2O_4$, then the resultant hydroquinone is reduced, e.g. with DIBAL-H, to the product.

For all aspects of the present invention halo is preferably fluoro or chloro.

The compounds, compositions, use, methods and intermediates of the invention will now be described by way of illustration only by reference to the following non-limiting Figures and Examples. Further embodiments of the invention will occur to those skilled in the art in the light of these.

Figures.

Figure 1: Shows the chemical structure of some known compounds referred to in the specific description above as compounds 1 to 5.

Figure 2: Shows the outline of the synthetic route used to prepare compounds 10, 11, 12 and 27, 28, 29 referred to herein.

Figure 3: Shows the outline of the synthetic route used to prepare compounds 13 to 42 referred to herein.

Figure 4: Shows the outline of the synthetic route used to prepare compounds 47 to 57 referred to herein.

Figure 5: Shows the outline of the synthetic route used to prepare compounds 58 to 66 referred to herein.

Figure 6: Is a graph plotting mean relative surviving RIF-1 tumour cell fraction against a a varying dose of compound 21 alone and against varying dose of compound 21 adminstered after 15 GY of radiation. The surviving fraction after 15 GY radiation alone is shown by a flat line.

Figure 7: Is a graph plotting mean relative surviving RIF-1 tumour cell fraction under conditions as set out for Figure 6 but using compound 54 as test compound.

Figure 8: Is a graph plotting mean relative surviving KHT tumour cell fraction against a varying dose of compound 21 alone and against a varying dose of compound 21 adminstered after 10 GY of radiation. The surviving fraction after 10 GY radiation alone is shown by a flat line.

Figure 9: Is a graph plotting mean relative surviving KHT tumour cell fraction under conditions as set out for Figure 8 but using compound 54 as test compound.

Definitions of the groups used in the Figures can be found in the text of Examples below and in the Figures themselves.

EXAMPLES

General methods for preparation of compounds 18 to 84:

2-Alkyl and cycloalkyl substituted indoles were synthesized in 14 steps from the common precursor 3-chlorophenol as shown in Figure 2 and 3. The crucial step was the 1,5-electrocyclisation of the imine (e.g. compound **8**) to the 2,3-dihydroindole derivatives, which was successfully carried out using isobutyraldehyde, cyclohexane carboxaldehyde or cyclopropane carboxaldeyde, but not with acrolein in a proposed alternative route, using zinc acetate in methanol as has been employed in the synthesis of EO9 via a 2-acrylate derivative in WO 87/06227. Nitration at the desired 4-position could be achieved only subsequent to the N-methylation step in order to avoid increasing yields of the 6-nitro isomer. The subsequent 6 steps, including nitration, oxidations (DDQ and Fremy's salt) and reductions (Sn/HCl, $LiAlH_4$, $Na_2S_2O_4$ and DIBAL-H) left the 2-cyclopropyl moiety intact and the desired indoloquinones were obtained. Substitution of the 5-methoxy substituent was successful in high yielding reactions with aziridine and 2-methylaziridine.

Comparable 1,2-dimethyl analogues **52-56** were synthesised from commercially available 2-methyl-5-methoxyindole in 7 steps (Figure 4). Substitution of the 5-position with aziridine and 2-methylaziridine was again succcessful in high yield, as was the *cis*-2,3-dimethylaziridine. However 2,2-dimethylaziridine reacted with difficulty and the resulting 5-(2,2-dimethylaziridinyl) analogue was unstable in aqueous solution and on silica gel, ring-opening via an S_N1 mechanism to give **57**. The 2-unsubstituted analogues **62-66** were obtained in 6 steps from 5-methoxyindole-3-carboxaldehyde (Figure 5).

NMR spectra were obtained at 90 MHz with a JEOL FX90Q spectrometer using $SiMe_4$ as internal standard. Elemental analyses were determined by Butterworth Laboratories Ltd., Teddington, Middlesex, U.K. Solutions in organic soivents were dried by treatment with $MgSO_4$ or Na_2SO_4 and filtration. Dichloromethane (CH_2Cl_2) was dried over calcium chloride and passed through neutral alumina prior to use. Dimethylformamide (DMF), toluene and tetrahydrofuran (THF) were anhydrous commercial grades. Silica gel for flash column chromatography was

Merck grade (230-400 mesh). Melting points were determined on a Thomas Hoover melting point apparatus and on a Thermogallen Microscope and Hot Stage Apparatus and are uncorrected. Stereochemically pure *cis*-2,3-dimethylaziridine and 2,2-dimethylaziridine were synthesized from the appropriately substituted 2-aminoethanols by *O*-sulfation and elimination with KOH according to the methods of Dickey *et al.* (see reference 19). Fused cyclopropamitosenes **4** and **5** were synthesized as described by Cotterill *et al.* (see reference 1) and O'Sullivan (see reference 20). Starting materials 2-chlorophenol, 5-methoxy-2-methylindole and 5-methoxyindole-3-carboxaldehyde were all purchased from Sigma-Aldrich Chemical Company.

Example 1: Preparation of 2-Cyclopropyl-3-methoxycarbonyl-5-methoxy-1-methylindole-4,7-dione (18) by reactions (v) to (xvii) of Figure 2.

(a) Diethyl 5-Methoxy-2-nitrophenylmalonate (6)

A solution of 17 g (0.064 mol) of ethyl 5-methoxy-2-nitrophenylcyanoacetate, prepared in 4 steps from 3-chlorophenyl as described by Speckamp and Oostveen (WO 87/06227), in EtOH (100 mL), was saturated with HCl gas on cooling in an ice/salt bath. The solution was stirred for 2 days and then ice-water (100 mL) added and the solution stirred for a further 24 hours at 4°C before the crystalline solid formed was collected by filtration, dried and recrystallized from EtOH to give 17 g (85%) of **6** as a white solid: mp 92-93°C (Lit. (Reference 4) 92-93°C).

(b) 2-Cyclopropyl-3,3-diethoxycarbonyl-2,3-dihydro-5-methoxyindole (9).

Compound **6** (5.0 g, 16.1 mmol) was dissolved in a mixture of toluene (62.5 mL) and EtOH (3.75 mL) and reduced with H_2 at atmospheric pressure over PtO_2 (75 mg) catalyst. After 7 hours at room temperature the solution was filtered through Celite and evaporated to dryness BELOW 30°C, and the resulting pale green oil (7) dissolved immediately in MeOH (75 mL). To this methanolic solution was added cyclopropane carboxaldehyde (1.3 g, 18.6 mmol) dissolved in MeOH (10 mL) and the solution stirred for 15 minutes. The resulting solution of imine **8** was treated *in situ* with $Zn(OAc)_2.2H_2O$ (1.13 g, 5.15 mmol) and stirred for 18 hours at room temperature.

The solution was evaporated to dryness at 30°C, HCl (2.0 M, 50 mL) added and extracted with CH_2Cl_2 (2 x 150 mL), washed with sat. $NaHCO_3$ (aq., 150 mL), sat. NaCl (aq., 100 mL), dried and evaporated. The residue was purified on silica, eluting with hexane/EtOAc (1:1, Rf=0.75) to give **9** (3.3 g, 68%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 0.48–0.52 (m, 4H, 2 x cyclopropyl-C*H*$_2$), 1.03-1.08 (m, 1H, cyclopropyl-*H*), 1.2 (t, 6H, J=7.2 Hz, CH_2CH_3), 1.3 (t, 6H, J=7.2 Hz, CH_2CH_3), 3.75 (s, 3H, C*H*$_3$O-), 3.85 (d, 1H, J=2.7 Hz, 2-H), 4.1-4.35 (m, 4H, CH_2CH_3), 6.63 (s, 1H, Ar-4*H*), 6.71 (d, 1H, J=1.5 Hz, Ar-6*H*) and 7.03 (d, 1H, J=1.5 Hz, Ar-7*H*).

(c) 1-Acetyl-2-cyclopropyl-3,3-diethoxycarbonyl-2,3-dihydro-5-methoxyindole (10).

Compound **9** (3.0 g, 10 mmol) was dissolved in Ac_2O (5 mL) and stirred for 3 hours at room temperature. The anhydride was then evaporated *in vacuo* and the residue purified on silica, eluting with hexane/EtOAc (2:1, Rf=0.4) to give a pale yellow oil which was redissolved in Et_2O and evaporated. Trituration of the resulting oil with Et_2O gave a white solid which was collected by filtration and washed with cold Et_2O to give **10** (3.0 g, 87%) as a white solid: mp 104-105°C; ^{1}H-NMR ($CDCl_3$) δ 0.5-0.57 (m, 4H, 2 x cyclopropyl-C*H*$_2$), 1.0-1.15 (m, 1H, cyclopropyl-*H*), 1.2 (t, 3H, J=7.2 Hz, CH_2CH_3), 1.3 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.81 (s, 3H, C*H*$_3$O-), 4.05-4.3 (m, 4H, CH_2CH_3), 4.5 (d, 1H, J=2.7 Hz, 2-*H*) and 6.9-7.2 (m, 3H, Ar-4,6,7*H*).

(d) 1-Acetyl-3-carboxy-2-cyclopropyl-2,3-dihydro-5-methoxyindole (11).

The acetylindole **10** (1.0 g, 2.9 mmol) was dissolved in EtOH (10 mL) and cooled to 0°C in an ice-salt bath, and a cold (0°C) solution of KOH (aq., 10%, 10 mL) was added. The solution was stirred at -5°C for 4 hours and then for 18 hours at 4°C. The solution was poured onto ice/water (25 mL) and washed with Et_2O. The aqueous layer was then acidified with 2.0 M HCl and extracted with $CHCl_3$ (6 x 50 mL), dried and evaporated to give 0.68 g (97%) of **11** as a yellow oil (Rf=0.45, Me_2CO), which was used in the next step without further purification; ^{1}H-NMR ($CDCl_3$) δ 0.5-0.7 (m, 4H, 2 x cyclopropyl-C*H*$_2$), 1.25-1.4 (m, 1H, cyclopropyl-*H*), 2.33 (s, 3H, COC*H*$_3$), 3.78 (s, 3H, C*H*$_3$O-), 3.85 (br, 1H, 3-*H*), 4.5 (br s, 1H, 2-*H*), 6.9-7.0 (m, 2H, Ar-4,6*H*), 8.05-8.15 (m, 1H, Ar-7*H*) and 10.81 (s, 1H, CO_2H).

(e) Methyl 1-acetyl-2-cyclopropyl-2,3-dihydro-5-methoxyindole-3-carboxylate (12).

To a solution of **11** (0.68 g, 2.8 mmol) in DMF (10 mL) was added K_2CO_3 (0.83 g, 6 mmol) and $(MeO)_2SO_2$ (2 g, 15.8 mmol) and the solution stirred at room temperature for 4 hours. The solution was then poured onto HCl (2.0 M, 20 mL) and extracted with $CHCl_3$ (4 x 25 mL), washed with sat. NaCl, dried and evaporated. The residue was purified on silica, eluting with EtOAC/hexane (1:2, Rf=0.7 (EtOAc)) to give a pale yellow oil of **12** (0.7g, 98%), which solidified on standing; ^{1}H-NMR ($CDCl_3$) δ 0.58–0.64 (m, 4H, 2 x cyclopropyl-CH_2), 1.25-1.33 (m, 1H, cyclopropyl-*H*), 2.33 (s, 3H, $COCH_3$), 3.68 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CH_3O-), 3.85 (br, 1H, 3-*H*), 4.54 (br, 1H, 2-*H*), 6.78-6.95 (m, 2H, Ar-4, 6*H*) and 8.2 (br s, 1H, Ar-7*H*).

(f) Methyl 1-acetyl-2-cyclopropyl-5-methoxyindole-3-carboxylate (13).

A solution of **12** (1.0 g, 4 mmol) was stirred under reflux with DDQ (0.96 g, 4.2 mmol) in toluene (12.5 mL) for 7 hours. The $DDQH_2$ was removed by filtration and the filtrate evaporated *in vacuo*. The residue was purified on silica, eluting with hexane/EtOAc (1:1, Rf=0.7) to give **13** (0.88 g, 87%) as a pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 0.73-0.79 (m, 2H, cyclopropyl-CH_2), 1.22-1.3 (m, 2H, cyclopropyl-CH_2), 2.15-2.25 (m, 1H, cyclopropyl-*H*), 2.83 (s, 3H, $COCH_3$), 3.86 (s, 3H, CO_2CH_3), 3.97 (s, 3H, CH_3O-), 6.99 (dd, 1H, J=2.7 and 9 Hz, Ar-6*H*), 7.5 (d, 1H, J=2.7 Hz, Ar-4*H*) and 7.96 (d, 1H, J=9 Hz, Ar-7*H*).

(g) Methyl 2-cyclopropyl-5-methoxyindole-3-carboxylate (14).

A solution of **13** (0.88 g, 3.46 mmol) in KOH (4% in MeOH, 50 mL) was stirred at room temperature for 1.5 hours, neutralized with 6.0M HCl and extracted with EtOAc (3 x 25 mL). The organic layer was washed with H_2O (50 mL), dried and evaporated to give **14** (0.51 g, 70%) as a white solid: mp 128-131°C; ^{1}H-NMR ($CDCl_3$) δ 0.82-0.92 (m, 2H, cyclopropyl-CH_2), 1.05-1.2 (m, 2H, cyclopropyl-CH_2), 2.2-3.0 (m, 1H, cyclopropyl-*H*), 3.85 (s, 3H, CO_2CH_3), 3.95 (s, 3H, CH_3O-), 6.79 (dd, 1H, J=2.7

and 9 Hz, Ar-6*H*), 7.22 (d, 1H, J=6.3 Hz, Ar-7*H*), 7.58 (d, 1H, J=2.7 Hz, Ar-4*H*) and 8.2 (br s, 1H, N*H*).

(h) Methyl 2-cyclopropyl-5-methoxy-1-methylindole-3-carboxylate (15).

Compound **14** (9.0 g, 42.6 mmol) was added under argon to a stirred suspension of NaH (6.0 g, 0.13 mol) in DMF (150 mL). The solution was heated at 45°C for 0.5 hours, cooled to 0-10°C and MeI (33 mL, 0.23 mol) added. The solution was then gradually heated to 60°C and stirred at this temperature for 1 hour, cooled and poured onto cold (0°C) $NaHSO_4$ (aq., 10%, 500 mL) and extracted with EtOAc (5 x 75 mL). The organic extracts were washed with sat. NaCl (150 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc/hexane (1:2, Rf=0.45) to give **15** (8.3 g, 86%) as a pale yellow waxy solid; ^{1}H-NMR ($CDCl_3$) δ 0.77-0.84 (m, 2H, cyclopropyl-C*H*$_2$), 1.21-1.29 (m, 2H, cyclopropyl-C*H*$_2$), 1.85-2.05 (m, 1H, cyclopropyl-*H*), 3.8 (s, 3H, C*H*$_3$N-), 3.86 (s, 3H, CO_2CH_3), 3.9 (s, 3H, C*H*$_3$O-), 6.86 (dd, 1H, J=2.7 and 9 Hz, Ar-6*H*), 7.23 (d, 1H, J=9 Hz, Ar-7*H*) and 7.62 (d, 1H, J=2.7 Hz, Ar-4*H*).

(i) Methyl 1-methyl-2-cyclopropyl-5-methoxy-4-nitroindole-3-carboxylate (16).

To a solution of **15** (8.0 g, 34.66 mmol) in AcOH (150 mL) cooled to 0°C, was added dropwise a cold (0°C) mixture of f.HNO_3 (27 mL) in AcOH (100 mL). The solution was stirred for 3 hours while allowing to reach room temperature, and then poured onto 300 g of crushed ice and after 15 minutes stirring the resulting yellow solid collected by suction filtration. The dried residue was purified on silica, eluting with EtOAc/hexane (1:1, Rf=0.45) to give 7.5 g (71%) of **16** as a yellow solid, recrystallised from EtOAc: mp 129-131°C; ^{1}H-NMR ($CDCl_3$) δ 0.74-0.81 (m, 2H, cyclopropyl-C*H*$_2$), 1.22-1.3 (m, 2H, cyclopropyl-C*H*$_2$), 1.85-2.05 (m, 1H, cyclopropyl-*H*), 3.8 (s, 3H, C*H*$_3$N-), 3.81 (s, 3H, CO_2CH_3), 3.89 (s, 3H, C*H*$_3$O-), 6.94 (d, 1H, J=9 Hz, Ar-7*H*) and 7.32 (d, 1H, J=9 Hz, Ar-6*H*).

(j) Methyl 4-amino-2-cyclopropyl-5-methoxy-1-methylindole-3-carboxylate (17). To a suspension of 2.5 g (9.25 mmol) **16** in EtOH (180 mL) were added tin powder (5.25 g, 44.2 mmol) and HCl (3.0 M, 70 mL) and the solution stirred at room temperature for 1 hour. The solution was then decanted from the excess tin and neutralized with sat. $NaHCO_3$ (aq.) and the resulting red suspension added to an equal volume of H_2O and extracted with $CHCl_3$ (5 x 50 mL) and then EtOAc (5 x 50 mL) and the combined extracts evaporated. The residue was purified on silica, eluting with EtOAc/hexane (1:1, Rf=0.5) to give **17** (2.2 g, 87%) as a white solid which was used immediately in the next step: mp 49-50°C; ^{1}H-NMR ($CDCl_3$) δ 0.65-0.72 (m, 2H, cyclopropyl-C*H*$_2$), 1.22-1.3 (m, 2H, cyclopropyl-C*H*$_2$), 1.8-1.9 (m, 1H, cyclopropyl-*H*), 3.73 (s, 3H, C*H*$_3$N-), 3.85 (s, 3H, CO_2CH_3), 3.9 (s, 3H, C*H*$_3$O-), 5.6 (br s, 1H, N*H*$_2$), 6.5 (d, 1H, J=9 Hz, Ar-7*H*) and 6.9 (d, 1H, J=9 Hz, Ar-6*H*).

(k) 2-Cyclopropyl-3-methoxycarbonyl-5-methoxy-1-methylindole-4,7-dione (18). To a solution of **17** (2.0 g, 7.2 mmol) in Me_2CO (250 mL) was added a solution of potassium nitrosodisulfonate ($(KSO_3)_2NO$, Fremy's salt, 9.7 g, 36.2 mmol)) in NaH_2PO_4/Na_2HPO_4 buffer (250 mL, 0.3 M, pH 6.0) and the solution stirred at room temperature for 1 hour. The Me_2CO was removed *in vacuo* and the resulting orange precipitate collected by suction filtration, washed with H_2O and dried in a vacuum oven at 45°C to afford **18** as an orange solid, recrystallized from EtOAc: mp 169-170°C; ^{1}H-NMR ($CDCl_3$) δ 0.69-0.77 (m, 2H, cyclopropyl-C*H*$_2$), 1.1-1.2 (m, 2H, cyclopropyl-C*H*$_2$), 1.48-1.58 (m, 1H, cyclopropyl-*H*), 3.80 (s, 3H, C*H*$_3$N-), 3.90 (s, 3H, CO_2CH_3), 4.01 (s, 3H, C*H*$_3$O-) and 5.64 (s, 1H, 6-*H*). Anal. C; 62.06, H; 5.20, N; 4.71%, Calc. ($C_{15}H_{15}NO_5$) C; 62.28, H; 5.19, N; 4.84%.

Example 2: 5-(Aziridin-1-yl)-2-cyclopropyl-3-methoxycarbonyl-1-methylindole-4,7-dione (19) by reaction (xviii) of Figure 2.

Compound **18** (0.29 g, 1 mmol) was dissolved and stirred in freshly redistilled 1(H)-aziridine (3 mL, ca.70 mmol, **CAUTION!**) for 1 hour, evaporated *in vacuo* and the residue redissolved in EtOAc. The solvent was then partially evaporated until a red precipitate appeared. The red solid was then collected by suction filtration and

recrystallized from EtOAc to afford **19** (0.25 g, 83%) as a red solid: mp 138-140°C; ^{1}H-NMR ($CDCl_3$) δ 0.65-0.72 (m, 2H, cyclopropyl-C*H*$_2$), 1.2-1.35 (m, 2H, cyclopropyl-C*H*$_2$), 1.7-1.8 (m, 1H, cyclopropyl-*H*), 2.18 (s, 4H, 2 x azir-C*H*$_2$), 3.92 (s, 3H, C*H*$_3$N-), 3.99 (s, 3H, CO_2CH_3 and 5.77 (s, 1H, 6-*H*). Anal. C; 63.60, H; 5.41, N; 9.33%, Calc. ($C_{16}H_{16}N_2O_4$) C; 64.00, H; 5.33, N; 9.33%.

Example 3: 2-Cyclopropyl-3-hydroxymethyl-5-methoxy-1-methylindole-4,7-dione (20) by reaction (xix) of Figure 2.

To a solution of **18** (0.3 g,1.03 mmol) in $CHCl_3$ (30 mL) and EtOH (11 mL) was added a solution of $Na_2S_2O_4$ (2.1 g, 12 mmol) in H_2O (13 mL). The solution was stirred at room temperature for 0.5 hour and the organic layer separated, washed with sat. NaCl (50 mL), dried and evaporated. The crude hydroquinone was then dissolved in anhydrous CH_2Cl_2 (30 mL) under argon and cooled to -30°C, and DIBAL-H (5 mL of a 1.5 M solution in toluene) added dropwise such that the solution temperature remained BELOW -30°C. The solution was then allowed to reach 0°C and stirred for 2.5 hours at this temperature, and a solution of $FeCl_3$ (9 mL, 1.0 M (0.1 M HCl)) added. The solution was stirred for 10 minutes at 0°C and then $CHCl_3$ (150 mL) and H_2O (150 mL) added. The aqueous layer was extracted with $CHCl_3$ (5 x 50 mL) then EtOAc (5 x 50 mL) and the combined organic phases washed with sat. NaCl (250 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc (Rf=0.5) to give **20** as an orange solid after recrystallization from EtOAc (125 mg, 47%): mp 200-202°C; ^{1}H-NMR ($CDCl_3$) δ 0.71-0.82 (m, 2H, cyclopropyl-C*H*$_2$), 1.2-1.33 (m, 2H, cyclopropyl-C*H*$_2$), 1.61-1.71 (m, 1H, cyclopropyl-*H*), 3.81 (s, 3H, C*H*$_3$N-), 3.98 (s, 3H, C*H*$_3$O-), 4.0 (br s, 1H, CH_2OH), 4.69 (br d, 2H, C*H*$_2$OH) and 5.64 (s, 1H, 6-*H*). Anal. C; 64.00, H; 5.66, N; 5.12%, Calc. ($C_{14}H_{15}O_4$); C; 64.36, H; 5.75, N; 5.36%.

Example 4: 5-(Aziridin-1-yl)-2-cyclopropyl-3-hydroxymethyl-1-methylindole-4,7-dione (21) by reaction (xx) of Figure 2.

Compound **20** (0.1 g, 0.38 mmol) was dissolved and stirred in freshly distilled **(CAUTION!)** 1(H)-aziridine (3 mL, ca. 70 mmol) for 0.75 hour, evaporated *in vacuo* and the residue redissolved in EtOAc, evaporated until a red precipitate appeared and the solid collected. The red solid was recrystallized from EtOAc to give **21** (80 mg, 77%): mp 177-179.5°C; ^{1}H-NMR ($CDCl_3$) δ 0.7-0.8 (m, 2H, cyclopropyl-C*H*$_2$), 1.22-1.3 (m, 2H, cyclopropyl-C*H*$_2$), 1.6-1.7 (m, 1H, cyclopropyl-*H*), 2.18 (s, 4H, 2 x azir-C*H*$_2$), 3.97 (s, 3H, C*H*$_3$N-), 4.73 (s, 2H, C*H*$_2$OH) and 5.77 (s, 1H, 6-*H*). Anal. C; 66.35, H; 5.61, N; 10.26%, Calc. ($C_{15}H_{16}N_2O_3$) C; 66.18, H; 5.88, N; 10.29%.

Example 5: 2-Cyclopropyl-3-hydroxymethyl-5-(2-methylaziridin-1-yl)-1-methyl-indole-4,7-dione (22) by reaction (xx) of Figure 2.

Compound **20** (0.1 g, 0.38 mmol) was dissolved and stirred in freshly distilled 2-methylaziridine (3 mL, ca. 50 mmol) for 2.5 hours. he solution was evaporated *in vacuo* and the residue redissolved in EtOAc, evaporated until a red precipitate appeared and the solid collected. The red solid was recrystallized from EtOAc to give **22** (85 mg, 78%): mp 130-131°C; ^{1}H-NMR ($CDCl_3$) δ 0.68-0.74 (m, 2H, cyclopropyl-CH_2), 1.08-1.2 (m, 2H, cyclopropyl-C*H*$_2$), 1.42 (d, 3H, J=4.5 Hz, azir-C*H*$_3$), 1.5-1.6 (m, 1H, cyclopropyl-*H*), 2.01-2.15 (m, 3H, azir-C*H*C*H*$_2$), 3.97 (s, 3H, C*H*$_3$N-), 4.73 (s, 2H, C*H*$_2$OH) and 5.74 (s, 1H, 6-*H*). Anal. C; 67.12, H; 6.04, N; 9.57%, Calc. ($C_{16}H_{18}N_2O_3$) C; 67.13, H; 6.29, N; 9.79%.

Example 6: 2-Cyclopropyl-5-methoxy-1-methyl-3-[[(phenoxycarbonyl)oxy]methyl] indole-4,7-dione (23) by reaction (xxi) of Figure 2.

To a solution of **20** (0.1 g, 0.38 mmol) in anhydrous pyridine (6 mL) at 0°C, was added dropwise phenylchloroformate (0.1 g, 0.64 mmol) and the solution then allowed to reach room temperature and stirred for 2 hours. The solution was then extracted with CH_2Cl_2 (25 mL) and washed with H_2O (25 mL) and sat. NaCl (25 mL), dried and

evaporated. The residue was purified on silica, eluting with EtOAc (Rf=0.75) to give **23** as an orange solid: mp 136-139°C; ^{1}H-NMR ($CDCl_3$) δ 1.02-1.18 (m, 2H, cyclopropyl-C*H*$_2$), 1.21-1.28 (m, 2H, cyclopropyl-C*H*$_2$), 1.78-1.88 (m, 1H, cyclopropyl-*H*), 3.79 (s, 3H, C*H*$_3$N-), 4.01 (s, 3H, C*H*$_3$O-), 5.27 (s, 2H, C*H*$_2$OCOPh), 5.51 (s, 1H, 6-*H*) and 7.15-7.3 (m, 5H, Ar).

Example 7: 2-Cyclopropyl-5-methoxy-1-methyl-3-[(carbamoyloxy)methyl] indole-4,7-dione (24) by reaction (xxii) of Figure 2.

The phenylcarbonate **23** (0.3 g, 0.78 mmol) was dissolved in anhydrous CH_2Cl_2 (38 mL) and the solution cooled to -78°C. The solution was then saturated with NH_3 and stirred at 78°C until reaction was complete (ca. 2 hours). The solution was then allowed to reach room temperature and evaporated *in vacuo*. The residue was redissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 x 100 mL) and sat. NaCl (50 mL), dried and evaporated, and the residue recrystallized from EtOAc to afford 220 mg (92%) of **24** as an orange solid: mp 240-242°C (dec.); ^{1}H-NMR ($CDCl_3$) δ 1.02-1.13 (m, 2H, cyclopropyl-C*H*$_2$), 1.22-1.26 (m, 2H, cyclopropyl-C*H*$_2$), 1.51-1.55 (m, 1H, cyclopropyl-*H*), 3.78 (s, 3H, C*H*$_3$N-), 3.99 (s, 3H, C*H*$_3$O-), 4.79 (br s, 2H, N*H*$_2$), 5.3 (s, 2H, C*H*$_2$OCONH$_2$) and 5.62 (s, 1H, 6-*H*).
Anal. C; 59.42, H; 4.88, N; 8.86%, Calc. ($C_{15}H_{16}N_2O_5$) C; 59.21, H; 4.88, N; 9.21%.

Example 8: 5-(Aziridin-1-yl)-2-cyclopropyl-1-methyl-3-[(carbamoyloxy)methyl] -indole-4,7-dione (25) by reaction (xxiii) of Figure 2.

The carbamate **24** (0.3 g,1.0 mmol) was stirred at room temperature in 1(H)-aziridine (2 mL, **CAUTION!**) for 15 minutes, evaporated and redissolved in EtOAc (5 mL). The solution was then evaporated to 50% volume and the resulting red precipitate filtered and washed well with cold EtOAc to afford **25** (210 mg, 63%) as a red solid: mp 235-238°C(dec.); ^{1}H-NMR ($(CD_3)_2SO$) δ 0.65-0.73 (m, 2H, cyclopropyl-C*H*$_2$), 1.05-1.15 (m, 2H, cyclopropyl-C*H*$_2$), 1.73-1.85 (m, 1H, cyclopropyl-*H*), 2.18 (s, 4H, 2 x azir-C*H*$_2$), 3.93 (s, 3H, C*H*$_3$N-), 5.06 (s, 2H, C*H*$_2$OCONH$_2$), 5.78 (s, 1H, 6-*H*) and 6.42 (br s, 2H, N*H*$_2$). Anal. C; 60.93, H; 5.60, N; 13.38%, Calc. ($C_{16}H_{17}N_3O_4$) C; 60.95, H; 5.39, N; 13.33%.

Example 9: 2-Cyclopropyl-1-methyl-5-(2-methylaziridin-1-yl)-3-[(carbamoyloxy)methyl]- indole-4,7-dione (26) by reaction (xxii) of Figure 2.

The carbamate **24** (0.05 g, 0.164 mmol) was stirred at room temperature in 2-methylaziridine (1.5 mL) for 4 hours, evaporated and redissolved in EtOAc (5 mL). The solution was then evaporated to 50% volume and the resulting red precipitate filtered and washed well with cold EtOAc, and then recrystallized from EtOAc to afford **26** (30 mg, 56%) as a red solid: mp 209-211°C(dec.); ^{1}H-NMR ($(CD_3)_2SO$) δ 0.63-0.72 (m, 2H, cyclopropyl-C*H*$_2$), 1.01-1.09 (m, 2H, cyclopropyl-C*H*$_2$), 1.29 (d, 3H, J=5.4Hz, azir-C*H*$_3$), 1.75-1.85 (m, 1H, cyclopropyl-*H*), 1.98-2.05 (m, 3H, azir-C*H*C*H*$_2$), 3.93 (s, 3H, C*H*$_3$N-), 5.06 (s, 2H, C*H*$_2$OCONH$_2$), 5.76 (s, 1H, 6-*H*) and 6.41 (br s, 2H, N*H*$_2$). Anal. C; 61.76, H; 5.41, N; 12.24%, Calc. ($C_{17}H_{19}N_3O_4$) C; 62.00, H; 5.77, N; 12.76%.

Example 10: Preparation of 2-Isopropyl-3-methoxycarbonyl-5-methoxy-1-methylindole-4,7-dione (35) by reactions (ix)-(xvii) of Figure 2.

(a) 1-Acetyl-3,3-diethoxycarbonyl-2,3-dihydro-2-isopropyl-5-methoxyindole (27). This compound was prepared (56%) by the method described for compound **9** but using isobutyraldehyde in place of cyclopropane carboxaldehyde. The residue after work-up was dissolved in Ac_2O (5 mL) and stirred for 3 hours at room temperature. The anhydride was then evaporated *in vacuo* and the residue purified on silica, eluting with hexane/EtOAc (1:1, Rf=0.5) to give **27** (87%) as a white solid: mp 77.5-78.5°C; ^{1}H-NMR ($CDCl_3$) δ 0.6 (d, 3H, J=7.2 Hz, CHC*H*$_3$), 0.9 (d, 3H, J=7.2 Hz, CHC*H*$_3$), 1.2 (t, 6H, J=7.2 Hz, CH$_2$C*H*$_3$), 1.3 (t, 6H, J=7.2 Hz, CH$_2$C*H*$_3$), 2.12-2.28 (m, 1H, C*H*(CH$_3$)$_2$), 2.36 (s, 3H, COC*H*$_3$), 3.81 (s, 3H, C*H*$_3$O-), 4.1-4.33 (m, 4H, 2 x C*H*$_2$CH$_3$), 4.8 (br, 1H, 2-*H*) and 6.9-7.8 (m, 3H, Ar-4,6,7*H*).

(b) 1-Acetyl-3-carboxy-2,3-dihydro-2-isopropyl-5-methoxyindole (28). The acetylindole **27** was hydrolysed as described for the preparation of **11** to give **28** (90%) as an off-white foam (Rf=0.45, Me_2CO), which was used in the next step without further purification; ^{1}H-NMR ($CDCl_3$) δ 0.59 (d, 3H, J=7.2 Hz, CHC*H*$_3$), 0.9 (d, 3H,

J=7.2 Hz, CHCH_3), 2.15-2.22 (m, 1H, CH(CH_3 $_2$), 2.2 (s, 3H, COCH_3), 3.72 (s, 3H, CH_3O-), 3.98 (br, 1H, 3-*H*), 4.62 (br, 1H, 2-*H*), 6.8-6.98 (m, 2H, Ar-4,7*H*) and 7.78-7.85 (m, 1H, Ar-6*H*).

(c) Methyl 1-acetyl-2,3-dihydro-2-isopropyl-5-methoxyindole-3-carboxylate (29).

In a procedure identical to that carried out on **11**, compound **29** was prepared from compound **28** as a pale brown oil (93%); ^{1}H-NMR ($CDCl_3$) δ 0.71 (d, 3H, J=7.2 Hz, CHCH_3), 1.0 (d, 3H, J=7.2 Hz, CHCH_3), 2.1-2.2 (m, 1H, CH(CH_3)$_2$), 2.32 (s, 3H, COCH_3), 3.69 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CH_3O-), 3.8 (br , 1H, 3-*H*), 4.6 (br, 1H, 2-*H*), 6.8-6.98 (m, 2H, Ar-4, 7*H*) and 7.78-7.85 (m, 1H, Ar-6*H*).

(d) Methyl 1-acetyl-2-isopropyl-5-methoxyindole-3-carboxylate (30).

A solution of **29** (1.0 g, 4.0 mmol) was stirred under reflux with DDQ (0.96 g, 4.2 mmol) in toluene (12.5 mL) for 2 days. The $DDQH_2$ was removed by filtration and the filtrate evaporated *in vacuo*. The residue was purified on silica, eluting with hexane/Me_2CO (3:1, Rf=0.65) to give **30** (0.44 g, 44%) as a pale red oil; ^{1}H-NMR ($CDCl_3$) δ 1.45 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 2.78 (s, 3H, COCH_3), 3.87 (s, 3H, CO_2CH_3), 3.96 (s, 3H, CH_3O-), 3.88-3.98 (m, 1H, CH(CH_3)$_2$), 6.89 (dd, 1H, J=2.7 and 9 Hz, Ar-6*H*), 7.44 (d, 1H, J=9 Hz, Ar-7*H*) and 7.55 (d, 1H, J=2.7 Hz, Ar-4*H*).

(e) Methyl 2-isopropyl-5-methoxyindole-3-carboxylate (31).

This compound was prepared from compound **30** as described for **14** (70%) as a pale red oil; ^{1}H-NMR ($CDCl_3$) δ 1.43 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 3.87 (s, 3H, CO_2CH_3), 3.92 (s, 3H, CH_3O-), 4.08-4.25 (m, 1H, CH(CH_3)$_2$), 6.9 (dd, 2H, J=2.7 and 9 Hz, Ar-6*H*), 7.1-7.6 (m, 2H, Ar-4,7*H*) and 8.2 (br s, 1H, N*H*).

(f) Methyl 2-isopropyl-5-methoxy-1-methylindole-3-carboxylate (32).

In a procedure identical to that carried out on **14**, compound **32** was prepared (80%) from compound **31** and purified on silica, eluting with EtOAc/hexane (1:2, Rf=0.74) as a pale yellow solid: mp 105-106°C; ^{1}H-NMR ($CDCl_3$)

δ 1.45 (d, 6H, J=7.2Hz, $CH(CH_3)_2$), 3.79 (s, 3H, CH_3N-), 3.88 (s, 3H, CO_2CH_3), 3.92 (s, 3H, CH_3O-), 4.22-4.45 (m, 1H, $CH(CH_3)_2$), 6.9 (dd, 2H, J=2.7 and 9Hz, Ar-6*H*) and 7.1-7.64 (m, 1H, Ar-4,7*H*).

(g) Methyl 2-isopropyl-5-methoxy-1-methyl-4-nitroindole-3-carboxylate (33).

To a solution of **32** (8.0 g, 34.66 mmol) in AcOH (150 mL) cooled to 0°C, was added dropwise a cold (0°C) mixture of f.HNO_3 (27 mL) in AcOH (100 mL). The solution was stirred for 3 hours while allowing to reach room temperature, and then poured onto 300 g of crushed ice and the resulting yellow solid collected by suction filtration. The dried residue was purified on silica, eluting with EtOAc/hexane (1:2, Rf=0.26) to give 7.5 g (71%) of **33** as a yellow solid, recrystallised from EtOAc: mp 149-150.5°C; ^{1}H-NMR ($CDCl_3$) δ 1.44 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 3.78 (s, 3H, CH_3N-), 3.82 (s, 3H, CO_2CH_3), 3.91 (s, 3H, CH_3O-), 3.95-4.15 (m, 1H, $CH(CH_3)_2$), 6.97 (d, 1H, J=9 Hz, Ar-6*H*) and 7.35 (d, 1H, J=9 Hz, Ar-7*H*).

(h) 2-Isopropyl-3-methoxycarbonyl-5-methoxy-1-methylindole-4,7-dione (35).

Compound **33** was reduced as described for **17** to give **34** (85%) and the crude material oxidized with Fremy's salt as described for **18.** After work-up the resulting orange precipitate was collected by suction filtration, washed with H_2O and dried in a vacuum oven at 45°C to afford **35** as an orange solid (75%), recrystallized from EtOAc: mp 192-194°C; ^{1}H-NMR ($CDCl_3$) δ 1.34 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 3.12-3.28 (m, 1H, $CH(CH_3)_2$), 3.81 (s, 3H, CH_3N-), 3.90 (s, 3H, CO_2CH_3), 3.97 (s, 3H, CH_3O-) and 5.64 (s, 1H, 6-H). Anal. C; 62.31, H; 5.82, N; 4.90% Calc. ($C_{15}H_{17}NO_5$) C; 61.86, H; 5.84, N; 4.81%.

Example 11: 3-Hydroxymethyl-2-isopropyl-5-methoxy-1-methylindole-4,7-dione (36) by reaction (xviii) of Figure 2.

To a solution of **35** (0.5 g, 1.7 mmol) in $CHCl_3$ (50 mL) and EtOH (18 mL) was added a solution of $Na_2S_2O_4$ (3.5 g, 20 mmol) in H_2O (22 mL). The solution was stirred at room temperature for 1hour and the organic layer separated, washed with sat. NaCl

(50 mL), dried and evaporated. The crude hydroquinone was dried over 18 hours *in vacuo* and then dissolved in anhydrous THF (5 mL) under argon and added to a solution of $LiAlH_4$ (12 mL of a 1.0 M solution inTHF) dropwise at room temperature and under argon. The solution was then stirred for 1 hour at 30°C, cooled to 0°C, and H_2O (15 mL) added dropwise, followed by a solution of $FeCl_3$ (12 mL, 1.0 M (0.1 M HCl)) added at 0°C. The solution was stirred for 10 minutes at 0°C and then EtOAc (150 mL) and H_2O (150 mL) added. The aqueous layer was extracted with EtOAc (5 x 50 mL) and the organic phase washed with sat. NaCl (250 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc/hexane, (1:1, Rf=0.22) to give, after recrystallization from EtOAc, **36** as an orange solid (140 mg, 31 %): mp 160-161°C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.82 (s, 3H, CH_3N-), 3.97 (s, 3H, CH_3O-), 4.71 (br, 2H, CH_2OH) and 5.64 (s, 1H, 6-*H*). Anal. C; 63.42, H; 6.50, N; 5.24% Calc. ($C_{14}H_{17}NO_4$) C; 63.88, H; 6.46, N; 5.32%.

Example 12: 5-(Aziridin-1-yl)-3-hydroxymethyl-2-isopropyl-1-methylindole-4,7-dione (37) by reaction (xx) of Figure 2.

A solution of **36** (50 mg, 0.19 mmol) in 1(H)-aziridine (0.5 mL, ca. 11.7 mmol, **CAUTION!**) was stirred for 0.5 hour at room temperature and then evaporated to dryness and the residue purified on silica, eluting with EtOAc (Rf=0.55) to give, after recrystallization from EtAOc, **37** (42 mg, 81%)) as a red solid: mp 144-145°C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 2.18 (s, 4H, 2 x azir-CH_2, 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.95 (s, 3H, CH_3N-), 4.68 (br s, 1H, CH_2OH), 4.76 (br, 2H, CH_2OH) and 5.76 (s, 1H, 6-*H*). Anal. C; 65.74, H; 6.64, N; 9.91% Calc. ($C_{15}H_{18}N_2O_3$) C; 65.69, H; 6.57, N; 10.22%.

Example 13: 3-Hydroxymethyl-2-isopropyl-5-(2-methylaziridin-1-yl)-1-methylindole-4,7-dione (38) by reaction (xx) of Figure 2.

Compound **36** (0.1 g, 0.38 mmol) was dissolved and stirred in freshly distilled 2-methylaziridine (3 mL, ca .50 mmol) for 2.5 hours. The solution was evaporated

in vacuo and the residue redissolved in EtOAc, evaporated and purified on silica (eluting with EtOAc) to afford a red glass (**38**, 85 mg, 78%): ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 1.42 (d, 3H, J=4.5 Hz, azir-CH_3), 2.01-2.15 (m, 3H, azir-$CHCH_2$), 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.95 (s, 3H, CH_3N-), 4.68 (br s, 1H, CH_2OH), 4.76 (br, 2H, CH_2OH) and 5.76 (s, 1H, 6-*H*). Anal. C; 67.12, H; 6.04, N; 9.57% Calc. ($C_{16}H_{20}N_2O_3$) C; 66.67, H; 6.94, N; 9.72%.

Example 14: Preparation of 2-isopropyl-5-methoxy-1-methyl-3-[(carbamoyloxy)-methyl]-indole-4,7-dione (40) by reactions (xxi) and (xxii) of Figure 2.

(a)2-Isopropyl-5-methoxy-1-methyl-3-[[(phenoxycarbonyl)oxy]methyl] indole-4,7-dione (39).

To a solution of **36** (0.55 g, 2.1 mmol) in anhydrous pyridine (25 mL) at 0°C, was added dropwise phenylchloroformate (0.5 g, 3.2 mmol) and the solution then allowed to reach room temperature and stirred for 1hour and then a further 0.25 g (1.6 mmoL) of phenylchloroformate was added. After a further 1 hour, H_2O (200 mL) was added and the solution was extracted with EtOAc (4 x 50 mL) and washed with H_2O (100 mL) and sat. NaCl (100 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc (Rf=0.8) to give **39** (0.6 g, 75%) as an orange solid: mp 126-127°C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 6H, J=7.2 Hz, $CH(CH_3)_2$), 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.79 (s, 3H, CH_3N-), 4.01 (s, 3H, CH_3O-), 5.27 (s, 2H, CH_2OCOPh), 5.51 (s, 1H, 6-*H*) and 7.15-7.3 (m, 5H, Ar).

(b) 2-Isopropyl-5-methoxy-1-methyl-3-[(carbamoyloxy)methyl] indole-4,7-dione (40).

The phenylcarbonate **39** (0.1 g, 0.26 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) and the solution cooled to -78°C. The solution was then saturated with NH_3 and stirred at -78°C until reaction was complete (ca. 2.5 hours). The solution was then allowed to reach room temperature and evaporated *in vacuo*. The residue was redissolved in CH_2Cl_2 (50 mL) and washed with H_2O (2 x 50 mL) and sat. NaCl (25 mL), dried and evaporated, and the residue recrystallized from EtOAc to afford

55 mg (69%) of **40** as an orange solid: mp 244-246°C (dec.); ^{1}H-NMR ($CDCl_3$) δ 1.37 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 3.1-3.28 (m, 1H, C*H*(CH$_3$)$_2$), 3.78 (s, 3H, CH_3N-), 3.99 (s, 3H, CH_3O-), 4.79 (br s, 2H, NH_2), 5.3 (s, 2H, CH_2OCONH$_2$) and 5.62 (s, 1H, 6-*H*). Anal. C; 58.67, H; 5.76, N; 9.02%, Calc. ($C_{15}H_{18}N_2O_5$) C; 58.82, H; 5.88, N; 9.15%.

Example 15: 5-(Aziridin-1-yl)-2-isopropyl-1-methyl-3-[(carbamoyloxy)methyl] indole-4,7-dione (41) by reaction (xxiii) of Figure 2.

The carbamate **40** (0.1 g, 0.33 mmol) was stirred at room temperature in 1(H)-aziridine (2 mL, **CAUTION!**) for 25 minutes, evaporated and redissolved in EtOAc (5 mL). The solution was then evaporated to 50% volume and the resulting red precipitate filtered and washed well with cold EtOAc to afford **41** (55 mg, 53%) as a red solid: mp 230-233°C(dec.); ^{1}H-NMR ((CD_3)$_2$SO) δ 1.37 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 2.18 (s, 4H, 2 x azir-CH_2), 3.1-3.28 (m, 1H, C*H*(CH$_3$)$_2$), 3.93 (s, 3H, CH_3N-), 5.06 (s, 2H, CH_2OCONH$_2$), 5.78 (s, 1H, 6-*H*) and 6.42 (br s, 2H, NH_2). Anal. C; 60.25, H; 6.04, N; 13.30%, Calc. ($C_{16}H_{19}N_3O_4$) C; 60.57, H; 5.99, N; 13.25%.

Example 16: 2-Isopropyl-1-methyl-5-(2-methylaziridin-1-yl)-3-[(carbamoyloxy)methyl] indole-4,7-dione (42) by reaction (xxiii) of Figure 2.

The carbamate **40** (0.1 g, 0.32 mmol) was stirred at room temperature in 2-methylaziridine (1.5 mL) for 2.5 hours, evaporated and redissolved in EtOAc (5 mL). The solution was then evaporated to 50% volume and the resulting red precipitate filtered and washed well with cold EtOAc, and then recrystallized from EtOAc to afford **42** (55 mg, 52%) as a red solid: mp 204-205°C(dec.); ^{1}H-NMR ((CD_3)$_2$SO) δ 1.37 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 1.42 (d, 3H, J=5.4 Hz, azir-CH_3), 1.98-2.05 (m, 3H, azir-C*H*C*H*$_2$), 3.1-3.28 (m, 1H, C*H*(CH$_3$)$_2$), 3.93 (s, 3H, CH_3N-), 5.06 (s, 2H, CH_2OCONH$_2$), 5.76 (s, 1H, 6-*H*) and 6.41 (br s, 2H, NH_2). Anal. C; 61.52, H; 6.36, N; 12.90%, Calc. ($C_{17}H_{21}N_3O_4$) C; 61.63, H; 6.34, N; 12.69%.

Example 17: 1,3-Dimethyl-2-isopropyl-5-methoxyindole-4,7-dione (43).

To a solution of **35** (0.5 g, 1.7 mmol) in $CHCl_3$ (50 mL) and EtOH (18 mL) was added a solution of $Na_2S_2O_4$ (3.5 g, 20 mmol) in H_2O (22 mL). The solution was stirred at room temperature for 1hour and the organic layer separated, washed with sat. NaCl (50 mL), dried and evaporated. The crude hydroquinone was dried over 18 hours *in vacuo* and then dissolved in anhydrous THF (5 mL) under argon and added to a solution of DIBAL-H (10 mL of a 1.5 M solution in toluene) dropwise at -30°C and under argon. The solution was then stirred for 18 hours at 4°C, cooled to 0°C, and H_2O (15 mL) added dropwise, followed by a solution of $FeCl_3$ (12 mL, 1.0 M (0.1 M HCl)) added at 0°C. The solution was stirred for 10 minutes at 0°C and then EtOAc (150 mL) and H_2O (150 mL) added. The aqueous layer was extracted with EtOAc (5 x 50 mL) and the organic phase washed with sat. NaCl (250 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc/hexane, (1: 2, Rf=0.44) to give, after recrystallization from EtOAc, **43** as an orange solid (48 mg, 11 %): mp 168-169°C; ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 2.38 (s, 3H, 3-CH_3), 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.78 (s, 3H, CH_3N-), 3.95 (s, 3H, CH_3O-) and 5.57 (s, 1H, 6-*H*).

Example 18: 5-(Aziridin-1-yl)-1,3-dimethyl-2-isopropylindole-4,7-dione (44).

A solution of **43** (30 mg, 0.12 mmol) in 1(H)-aziridine (0.5 mL, ca. 11.7 mmol, **CAUTION!**) was stirred for 0.5 hour at room temperature and then evaporated to dryness and the residue purified on silica, eluting with EtOAc/hexane (1:2, Rf=0.32) to give, after recrystallization from EtAOc, **44** (5.5 mg, 18%)) as a red solid: mp 110-112°C; ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 6H, J=7.2 Hz, CH(CH_3)$_2$), 2.15 (s, 4H, 2 x azir-CH_2), 2.38 (s, 3H, 3-CH_3), 3.1-3.28 (m, 1H, $CH(CH_3)_2$), 3.94 (s, 3H, CH_3N-) and 5.72 (s, 1H, 6-*H*).

Example 19: 2-Cyclohexyl-3-hydroxymethyl-5-methoxy-1-methylindole-4,7-dione (45).

The corresponding 3-methoxycarbonyl precursor compound was prepared as described for **18** and **35** but using cyclohexylcarboxaldehyde in the in-line cyclisation step and the subsequent oxidation step with DDQ required a much prolonged reaction time of 12h. The crude 4-amino compound was again oxidized with Fremy's salt as described for **18**. After work-up the resulting orange precipitate was collected by suction filtration, washed with H20 and dried in a vacuum oven at 45°C to give 2-cyclohexyl-3-methoxycarbonyl-5-methoxy-1-methylindole-4,7-dione as an orange solid (75%), recrystallized from EtOAc: mp 190-192°C; ^{1}H-NMR ($CDC1_3$) 8 1.27 (m, 6H, 6 x cylohexyl-H), 1.83 (m, 5H, 5 x cyclohexyl-H), 3.79 (s, 3H, CH_3N-), 3.91 (s, 3H, CO_2CH_3), 3.96 (s, 3H, CH_3O-) and 5.63 (s, IH, 6-H). This compound was then reduced with $LiAlH_4$ as described for **36** to give **45** as an orange solid (59 %): mp 214-215°C; ^{1}H-NMR ($CDC1_3$) & 1.25 (m, 6H, 6 x cylohexyl-H), 1.78 (m, 5H, 5 x cyclohexyl-H), 3.81 (s, 3H, CH_3N-), 3.97 (s, 3H, CH_3O-), 4.76 (s, 2H, CH_2OH) and 5.63 (s, IH, 6-H). Anal. C; 67.54, H; 6.82, N; 4.67% Calc. ($C_{17}H_{21}NO_4$) C; 67.31, H; 6.98, N; 4.62%.

Example 20: 5-(Aziridin-1-yl)-2-cyclohexyl-3-hydroxymethyl-1-methylindole-4,7-dione (46).

A solution of **45** (30mg,0.1mmol) infreshly distilled 1(H)-aziridine (0.5mL, ca. 11.7mmol, **CAUTION** !) was stirred for 0.5h at room temperature and then evaporated to dryness and the residue purified on silica, eluting with EtOAc/hexane. (1:1, Rf=0.3) to a give, after recrystallization from EtAOc, **46** (22mg, 70%)) as a red solid: mp 128-130°C; ^{1}H-NMR ($CDC1_3$) 8 1.26 (m, 6H, 6 x cylohexyl-H), 1.78 (m, 5H, 5 x cyclohexyl-H), 2.18 (s, 4H, 2 x aziridine-CH_2), 3.95 (s, 3H, CH_3N-), 4.76 (s, 2H, CH2OH) and 5.77 (s, IH, 6-H). Anal. C; 63.72, H; 6.97, N; 8.22% Calc. ($C_{18}H_{22}N_20_3.1.5H_2O$)C; 63.34, H; 7.33, N; 8.21%.

Example 21:Preparation of 5-Methoxy-3-hydroxymethyl-1,2-dimethylindole-4,7-dione (52) by reactions (i) to (vi) of Figure 3.

(a) 5-Methoxy-1,2-dimethylindole (47).

5-Methoxy-2-methylindole (10 g, 0.062 mol) was added gradually and under dry argon to a stirred suspension of NaH (2.73 g of a 60% dispersion, 0.068 mol) in DMF (150 mL). The suspension was heated at 45°C for 10 minutes, cooled to room temperature, and MeI (33 mL, 0.23 mol) added over 5 minutes. The solution was then heated at 60°C for 1 hour, cooled and poured onto cold (0°C) $NaHSO_4$ (aq., 10%, 150 mL) and extracted with EtOAc (3 x 100 mL), dried and evaporated. The residue was purified on silica, eluting with 3% EtOAc/hexane (Rf=0.5) to give 4.5 g (41%) of **45** as a pale brown solid: mp 73-74°C; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H, 2-C*H*$_3$), 3.59 (s, 3H, C*H*$_3$N-), 3.82 (s, 3H, C*H*$_3$O-), 6.16 (s, 1H, 3-*H*) and 6.9-7.28 (m, 3H, Ar-4,6,7*H*).

(b) 5-Methoxy-1,2-dimethylindole-3-carboxaldehyde (48).

N-methylformanilide (0.95 g, 7.04 mmol) and $POCl_3$ (1.08 g, 7.05 mmol) were stirred at room temperature until the yellow solid chloroimmonium Vilsmeier compound formed. The yellow solid was then added to a solution of **47** (0.7 g, 4 mmol) in 1,2-dichloroethane (15 mL) and the solution heated under reflux for 1.5 hours, cooled, and NaOAc (1.0 M, 50 mL) added. The solution was extracted with EtOAc (4 x 100 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc/hexane (1:1, Rf=0.5 (EtOAc)) to give 0.35 g (43%) of **48** as an off-white solid: mp 108-110°C; ^{1}H-NMR ($CDCl_3$) δ 2.62 (s, 3H, 2-C*H*$_3$), 3.63 (s, 3H, C*H*$_3$N-), 3.89 (s, 3H, C*H*$_3$O), 6.94-7.2 (m, 2H, Ar-6,7H), 7.8 (d, 1H, J=2 Hz, Ar-4*H*) and 10.1 (s, 1H, C*H*O).

(c) 5-Methoxy-1,2-dimethyl-4-nitroindole-3-carboxaldehyde (49) by reaction (iii).

Compound **48** (6.0 g, 0.03 mol) was dissolved in AcOH (480 mL) and cooled to 5°C and f.HNO_3 (18 mL) in AcOH (72 mL) added dropwise with stirring over 5 minutes. The solution temperature was allowed to rise to 20°C over 18 hours and the mixture

poured on to crushed ice (500 g) and the yellow precipitate collected by suction filtration and dried *in vacuo* at 50°C. The yellow solid was purified on silica, eluting with EtOAc/hexane (2:1, Rf=0.42 (EtOAc)) to give 4.37 g (59%) of **49** as a pale yellow solid: mp 236-238°C(dec.); ^{1}H-NMR ($(CD_3)_2SO$) δ 2.71 (s, 3H, 2-C*H*$_3$), 3.76 (s, 3H, C*H*$_3$N-), 3.89 (s, 3H, C*H*$_3$O), 7.25 (d, 1H, J=9 Hz, Ar-7H), 7.75 (d, 1H, J=9 Hz, Ar-6*H*) and 9.9 (s, 1H, C*H*O).

(d) 4-Amino-5-methoxy-1,2-dimethylindole-3-carboxaldehyde (50) by reaction (iv). Nitro-compound **49** (0.18 g, 0.74 mmol) was dissolved in EtOH (15 mL) and powdered tin (0.45 g, 3.8 mmol) added, followed by HCl (3.0 M, 5.6 mL) and the solution heated under gentle reflux for 1hour. Water (50 mL) was added and the solution neutralized with $NaHCO_3$ (aq.) and then extracted with $CHCl_3$ (3 x 100 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc/hexane (1:1, Rf=0.57 (EtOAc)) to give 0.1 g (62%) of **50** as a pale yellow solid: mp 152-153°C (dec.); ^{1}H-NMR ($(CD_3)_2SO$) δ 2.61 (s, 3H, 2-C*H*$_3$), 3.59 (s, 3H, C*H*$_3$N-), 3.75 (s, 3H, C*H*$_3$O), 6.0 (br s, 2H, N*H*$_2$), 6.56 (d, 1H, J=9 Hz, Ar-7H), 6.85 (d, 1H, J=9 Hz, Ar-6*H*) and 9.71 (s, 1H, C*H*O).

(e) 5-Methoxy-1,2-dimethyl-4,7-dioxoindole-3-carboxaldehyde (51). To a solution of **50** (0.074 g, 0.34 mmol) in Me_2CO (14 mL) was added a solution of Fremy's salt (0.45 g, 1.68 mmol) in NaH_2PO_4/Na_2HPO_4 buffer (14 mL, 0.3 M, pH 6.0) and the solution stirred at room temperature for 1 hour. The solution was evaporated at 30°C to remove most of the Me_2CO and the resulting orange precipitate collected by suction filtration and washed well with H_2O and cold MeOH, to give **51** (0.06 g, 75%): mp 239-242°C; ^{1}H-NMR ($(CD_3)_2SO$) δ 2.5 (s, 3H, 2-C*H*$_3$), 3.82 (s, 3H, C*H*$_3$N-), 3.88 (s, 3H, C*H*$_3$O), 5.89 (s, 1H, 6-*H*) and 10.37 (s, 1H, C*H*O).

(f) 5-Methoxy-3-hydroxymethyl-1,2-dimethylindole-4,7-dione (52) by reaction (vi). To a suspension of **51** (0.25 g, 0.94 mmol) in MeOH (100 mL, degassed by boiling in under argon *in vacuo*) was added $NaBH_4$ (0.36 g, 9.7 mmol) while maintaining a dry

argon atmosphere. The solution was stirred at room temperature for 1 hour and the solution aerated prior to the addition of H_2O (40 mL) and the solution extracted with CH_2Cl_2 (3 x 100 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc (Rf=0.4) to afford **52** (0.1 g, 33%) as an orange solid, recrystallized from EtOAc: mp 215-216°C; ^{1}H-NMR ($CDCl_3$) δ 2.21 (s, 3H, 2-CH_3), 3.81 (s, 3H, CH_3N-), 3.86 (s, 3H, CH_3O), 4.65 (br d, 2H, J=7.2 Hz, CH_2OH) and 5.61 (s, 1H, 6-*H*)

Example 22: 5-(Aziridin-1-yl)-3-hydroxymethyl-1,2-dimethylindole-4,7-dione (53) via reaction (vii) of Figure 4.

A solution of **52** (235 mg, 1.0 mmol) in freshly redistilled 1(H)-aziridine (1.5 mL, ca. 35 mmol, **CAUTION!**) was stirred for 0.5 hour at room temperature and evaporated *in vacuo*. The residue was redissolved in EtOAc, condensed by 75%, and the precipitate collected and washed with cold EtOAc, to give 225 mg (91%) of **53** as a dark red solid: mp 173-174°C (dec.); ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 4H, 2 x azir-CH_2), 2.22 (s, 3H, 2-CH_3), 3.86 (s, 3H, CH_3N-), 3.95 (br, 1H, CH_2O*H*), 4.65 (br d, 2H, CH_2OH) and 5.76 (s, 1H, 6-*H*). Anal. C; 63.08, H; 5.62, N; 11.07% Calc. ($C_{13}H_{14}N_2O_3$) C; 63.41, H; 5.69, N; 11.38%.

Example 23 : 3-Hydroxymethyl-5-(2-methylaziridin-1-yl)-1,2-dimethylindole-4,7-dione (54) by reaction (vii) of Figure 4.

A solution of **52** (235 mg, 1.0 mmol) in 2-methylaziridine (2 mL, ca. mmol) was stirred at room temperature for 4 hours and worked up as described for **53** to give **54** (195 mg, 75%) as a dark red solid: mp 120-122°C; ^{1}H-NMR ($CDCl_3$) δ 1.42 (d, 3H, *J*=5.4 Hz, azir-CH_3), 2.08-2.21 (m, 3H, azir-$CHCH_2$), 2.22 (s, 3H, 2-CH_3), 3.89 (s, 3H, CH_3N-), 4.61 (br, 1H, CH_2O*H*), 4.63 (br, 2H, CH_2OH) and 5.75 (s, 1H, 6-*H*). Anal. C; 65.09, H; 5.79, N; 10.72% Calc. ($C_{14}H_{16}N_2O_3$) C; 64.61, H; 6.15, N; 10.77%.

Example 24: 3-Hydroxymethyl-5-(*cis*-2,3-dimethylaziridin-1-yl)-1,2-dimethylindole-4,7-dione (55) by reaction (vii) of Figure 4.

A solution of **52** (100 mg, 0.43 mmol) in cis-2,3-dimethylaziridine (2 mL) was stirred for 1 hour at room temperature and then evaporated *in vacuo* at 30°C. The residue was purified on silica, eluting with EtOAc (Rf=0.6), to give **55** (65 mg, 55%) after recrystallization from EtOAc: mp 132-135°C; ^{1}H-NMR ($CDCl_3$) δ 1.38 (d, 6H, *J*=5.4Hz, 2 x azir-C*H*$_3$), 2.15-2.21 (m, 2H, 2 x azir-C*H*), 2.22 (s, 3H, 2-C*H*$_3$), 3.85 (s, 3H, C*H*$_3$N-), 4.24 (br, 1H, CH$_2$O*H*), 4.63 (br, 2H, C*H*$_2$OH) and 5.73 (s, 1H, 6-*H*). Anal. C; 65.93, H; 6.50, N; 10.12% Calc. ($C_{15}H_{18}N_2O_3$) C; 65.69, H; 6.57, N; 10.22%.

Example 25: 3-Hydroxymethyl-5-(2,2-dimethylaziridin-1-yl)-1,2-dimethylindole-4,7-dione (56) by reaction (viii) of Figure 4.

A solution of **52** (100 mg, 0.43 mmol) in 2,2-dimethylaziridine (2 mL) was stirred at 95°C for 5 hours. After this time (reaction does not go to completion) the solution was cooled and evaporated *in vacuo*, and the residue redissolved in EtOAc and evaporated to precipitate **56** as a dark red solid, which was unstable on silica and in solution: mp 138-141°C; ^{1}H-NMR ($CDCl_3$) δ 1.32 (s, 6H, 2 x azir-C*H*$_3$), 2.07 (s, 2H, azir-C*H*$_2$), 2.22 (s, 3H, 2-C*H*$_3$), 3.87 (s, 3H, C*H*$_3$N-), 4.25 (br, 1H, CH$_2$O*H*), 4.86 (br, 2H, C*H*$_2$OH) and 5.68 (s, 1H, 6-*H*). Anal. C; 62.92, H; 6.88, N; 9.58% Calc. ($C_{15}H_{18}N_2O_3.2/3H_2O$) C; 62.94, H; 6.76, N; 9.79%.

Example 26: 3-Hydroxymethyl-5-(2,2-dimethyl-2-hydroxyethyl)amino)-1,2-dimethylindole-4,7-dione (57) by reaction (viii) of Figure 4.

Compound **56** (25 mg, mmol) was dissolved in 5 mL H_2O with warming to 45°C and then evaporated *in vacuo* at 50°C. The residue was purified on silica, eluting with EtOAc (Rf=0.35) to give **57**, after recrystallization from EtOAc: mp 188-190°C; ^{1}H-NMR ($(CD_3)_2SO$) δ 1.14 (s, 6H, 2 x C*H*$_3$), 2.21 (s, 3H, 2-C*H*$_3$), 3.02 (d, 2H, J=7.2 Hz, NHC*H*$_2$C(CH$_3$)$_2$), 3.84 (s, 3H, C*H*$_3$N-), 4.58 (br, 2H, C*H*$_2$OH), 4.65 (br, 1H, CH$_2$O*H*), 5.14 (s, 1H, 6-*H*) and 6.63 (br t, 1H, N*H*). Anal. C; 60.62, H; 6.96, N; 9.34% Calc. ($C_{15}H_{20}N_2O_4.1/3H_2O$) C; 60.40, H; 6.94, N; 9.39%.

Example 27: Preparation of 3-Hydroxymethyl-5-(2-methylaziridin-1-yl)-1-methyl-indole-4,7-dione (62) by reactions (I) to (v) of Figure 5.

(a) 5-Methoxy-1-methylindole-3-carboxaldehyde (58).

5-methoxyindole-3-carboxaldehyde (2.0 g, 11.4 mmol) was added portionwise to a suspension of NaH (0.55 g, 13.7 mmol) in DMF (50 mL) with stirring. The suspension was stirred for 0.5 hour, and MeI (1.94 g, 13.7 mmol) added and the mixture stirred for 1 hour at room temperature. The reaction mixture was then poured on to $NaHCO_3$ (10%, 300 mL) and extracted wih EtOAc (4 x 75 mL), washed with $NaHCO_3$ (10%, 3 x 50 mL), sat. NaCl (3 x 100 mL), dried and evaporated *in vacuo* to give **58** (1.70 g, 79%) as a white solid: mp 132-133°C; ^{1}H-NMR ($CDCl_3$) δ 3.81 (s, 3H, C*H*$_3$N-), 3.89 (s, 3H, C*H*$_3$O-), 7.08 (dd, 1H, J=2 and 9 Hz, Ar-6H), 7.31 (d, 1H, J=9 Hz, Ar-7H), 7.59 (s, 1H, 2-H), 7.8 (d, 1H, J=2 Hz, Ar-4*H*) and 9.93 (s, 1H, C*H*O).

(b) 5-Methoxy-1-methyl-4-nitroindole-3-carboxaldehyde (59).

To a solution of **56** (1.50 g, 7.94 mmol) dissolved in AcOH (150 mL) was added a mixture of c.HNO_3 (4.5 mL) in AcOH (25 mL) dropwise at 0°C over 3 hours. After addition, the mixture was stirred at room temperature for 16 hours, and then added to crushed ice (75 g), filtered and washed with H_2O (5 x 100 mL) and dried to give **57** (1.56 g, 84%) as a pale yellow solid: mp 197-198°C; ^{1}H-NMR ($(CD_3)_2SO$) δ 3.94 (s, 6H, C*H*$_3$O- and C*H*$_3$N-), 7.32 (d, 1H, *J*=9 Hz, Ar-7*H*), 7.72 (d, 1H, *J*=9 Hz, Ar-6*H*), 8.27 (s, 1H, 2-*H*) and 9.75 (s, 1H, C*H*O).

(c) 4-Amino-5-methoxy-1-methylindole-3-carboxaldehyde (60).

To a suspension of **59** (1.0 g, 4.27 mmol) in EtOH (150 mL) was added tin (4.43 g, 37 mmol) followed by HCl (3.0 M, 60 mL). The mixture was stirred at room temperature for 2 hours and decanted. The solution was added portionwise to sat. $NaHCO_3$ (aq., 300 mL). and extracted with EtOAc (3 x 100 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (aq., 2 x 175 mL), sat. NaCl (3 x 75 mL), dried and evaporated *in vacuo* to give **60** (0.79 g, 91%) as a dark yellow solid which was used in the next step without further purification; Rf=0.64 (EtOAc);

^{1}H-NMR ($CDCl_3$) δ 3.75 (s, 3H, C*H*$_3$N-), 3.88 (s, 3H, C*H*$_3$O-), 5.79 (br s, 2H, N*H*$_2$), 6.56 (d, 1H, *J*=9 Hz, Ar-7*H*), 7.53 (d, 1H, *J*=9 Hz, Ar-6*H*), 7.64 (s, 1H, 2-*H*) and 9.60 (s, 1H, C*H*O).

(d) 5-methoxy-1-methyl-4,7-dioxoindole-3-carboxaldehyde (61).

To **60** (0.75 g, 3.68 mmol) dissolved in Me_2CO (75 mL) was added Fremy's salt (4.0 g, 14.9 mmol) in H_2O (20 mL) followed by a solution of Na_2HPO_4/NaH_2PO_4 buffer (0.3 M, pH 6, 20 mL). The mixture was stirred for 0.75 hour, excess Me_2CO removed and the product filtered and washed with H_2O (50 mL), dried, and recrystallized from EtOAc to give **61** (0.61 g, 76%) as a yellow solid: mp 188-190°C; ^{1}H-NMR ($CDCl_3$) δ 3.87 (s, 3H, C*H*$_3$N-), 4.02 (s, 3H, C*H*$_3$O-), 5.78 (s, 1H, 6-*H*), 7.44 (s, 1H, 2-*H*) and 10.54 (s, 1H, C*H*O).

(e) 3-Hydroxymethyl-5-methoxy-1-methylindole-4,7-dione (62).

To a solution of **61** (0.5 g, 2.28 mmol) in anhydrous MeOH (300 mL) was added $NaBH_4$ (0.65 g, 17 mmol). The solution was degassed with argon and stirred for 2 hours under argon and then evaporated *in vacuo* to give a solid which was diluted with CH_2Cl_2 (300 mL) and washed with H_2O (2 x 100 mL), sat. NaCl (100 mL) and condensed to give **62** as an orange solid (0.2 g, 40%) after recrystallization from EtOAc: mp 185-186°C; ^{1}H-NMR ($CDCl_3$) δ 3.85 (s, 3H, C*H*$_3$N-), 3.94 (s, 3H, C*H*$_3$O-), 4.25-4.29 (m, 2H, C*H*$_2$OH), 5.73 (s, 1H, 6-*H*) and 6.88 (s, 1H, 2-*H*). Anal. C; 59.84, H; 4.79, N; 6.30% Calc. ($C_{11}H_{11}NO_4$) C; 59.73, H; 4.98, N; 6.33%.

Example 28: Preparation of 5-(Aziridin-1-yl)-3-hydroxymethyl-1-methylindole-4,7-dione (63) by reaction (vi) of Figure 5.

A solution of **62** (200 mg, 0.9 mmol) in 1(H)-aziridine (1.5mL, ca. 35 mmol, **CAUTION!**) was stirred at room temperature for 1.5 hours. Excess aziridine was removed *in vacuo*, and the product was recrystallized from EtOAc to give **63** (130 mg, 62%) as an orange solid: mp 169-171°C; ^{1}H-NMR ($CDCl_3$) δ 2.22 (s, 4H, 2 x aziridine-C*H*$_2$), 3.91 (s, 3H, C*H*$_3$N-), 4.64 (s, 2H, C*H*$_2$OH), 5.81 (s, 1H, 6-*H*),

and 6.69 (s, 1H, 2-*H*). Anal. C; 61.47, H; 5.14, N; 12.22% Calc. ($C_{12}H_{12}N_2O_3$) C; 62.07, H; 5.17, N; 12.07%.

Example 29: Preparation of 3-Hydroxymethyl-5-(2-methylaziridin-1-yl)-1-methyl-indole-4,7-dione (64) by reaction (vi) of Figure 5.

A solution of **62** (200 mg, 0.9 mmol) in 2-methylaziridine (1 mL) was stirred at room temperature for 2.5 hours. Excess 2-methylaziridine was removed *in vacuo*, and the product was purified on silica, eluting with EtOAc (Rf=0.6) to give **64** (120 mg, 54%) as a red solid recrystallized from EtOAc: mp 89-90°C; ^{1}H-NMR ($CDCl_3$) δ 1.47 (d, 3H, *J*=4.5 Hz, azir-CH_3), 2.04-2.2 (m, 3H, azir-CHCH_2), 3.91 (s, 3H, N-CH_3), 4.67 (m, 2H, CH_2OH), 5.79 (s, 1H, 6-*H*) and 6.70 (s, 1H, 2-*H*).

Example 30: Preparation of 5-methoxy-1-methyl-3-[(carbamoyloxy)methyl] indole-4,7-dione (65) by reaction (vii) of Figure 5.

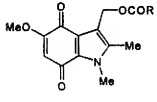
To a solution of **62** (0.1 g, 0.45 mmol) in anhydrous pyridine (5 mL) at 0°C, was added dropwise phenylchloroformate (0.1 g, 0.64 mmol) and the solution then allowed to reach room temperature and stirred for 2 hours. The solution was then extracted with CH_2Cl_2 (30 mL) and washed with H_2O (35 mL) and sat. NaCl (35 mL), dried and evaporated. The residue was purified on silica, eluting with EtOAc (Rf=0.8) to give an orange solid of 5-methoxy-1-methyl-3-[[(phenoxycarbonyl)oxy]methyl] indole: mp 85-86°C; ^{1}H-NMR ($(CD_3)_2SO/CDCl_3$) δ 3.79 (s, 3H, CH_3N-), 3.91 (s, 3H, CH_3O-), 5.43 (s, 2H, CH_2OCOPh), 5.67 (s, 1H, 6-*H*), 6.89 (s, 1H, 2-*H*) and 7.15-7.3 (m, 5H, Ar). This material (0.1 g, 0.3 mmol) was dissolved in anhydrous CH_2Cl_2 (18 mL) and the solution cooled to -78°C. The solution was then saturated with NH_3 and stirred at -78°C until reaction was complete (0.75 hour). The solution was then allowed to reach room temperature and evaporated *in vacuo*. The residue was redissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 x 100 mL) and sat. NaCl (50 mL), dried and evaporated, and the residue recrystallized from EtOAc to afford 75 mg (98%) of **65** as an orange solid: mp 231-234°C (dec.); ^{1}H-NMR ($(CD_3)_2SO/CDCl_3$) δ 3.78 (s, 3H, CH_3N-), 3.88 (s, 3H, CH_3O-),

5.04 (s, 2H, CH_2OCONH_2), 5.77 (s, 1H, 6-*H*), 6.42 (br s, 2H, NH_2) and 7.09 (s, 1H, 2-*H*). Anal. C; 54.98, H; 4.56, N; 10.18%, Calc. ($C_{12}H_{12}N_2O_5$) C; 54.55, H; 4.55, N; 10.61%.

Example 31: Preparation of 5-(Aziridin-1-yl)-1-methyl-3-[(carbamoyloxy)methyl] indole-4,7-dione (66) by reaction (viii) of Figure 5.

Compound **65** (50 mg, 0.2 mmol) was stirred for 0.5 hour in 1(*H*)-aziridine (ca. 35 mmol), evaporated *in vacuo* and redissolved in EtOAc. The solution was evaporated again and the residue recrystallized from EtOAc to afford 35 mg (70%) of **66** as a red solid: mp 195-198°C (dec.); ^{1}H-NMR ($(CD_3)_2SO$) δ 2.18 (s, 4H, 2 x azir-CH_2), 3.90 (s, 3H, CH_3N-), 5.23 (s, 2H, CH_2OCONH_2), 5.49 (br s, 2H, NH_2) 5.76 (s, 1H, 6-*H*) and 6.86 (s, 1H, 2-*H*). Anal. C; 56.70, H; 4.94, N; 15.35%, Calc. ($C_{13}H_{13}N_3O_4$) C; 56.73, H; 4.73, N; 15.27%.

Further compounds were pepared in order to investigate the effect of different leaving groups at the R^1 position in Formula I; these compounds being divided into three formula options A, B and C and the corresponding chloromethyl compound. By keeping the groups R, R^2 and R^3 methyl and R^4 hydrogen, as in Examples 32 to 44 and 46 to 49, bioassay could be used to evaluate the effect of different leaving groups. Example 45 describes a preferred compound where R^2 is cyclopropyl.



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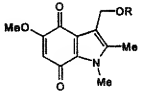

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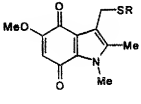


C

Example 32: Preparation of 3-Chloromethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (67)

5-Methoxy-3-hydroxymethyl-1,2-dimethylindole-4,7-dione (**52**, 500mg, 1.97mmol) was stirred at room temperature with 5mL $SOCl_2$ for 0.5h. The solution was then evaporated *in vacuo*, redissolved in EtOAc (25mL) and evaporated to dryness. This procedure was repeated twice and the crude orange solid (0.43 g, 85%) of 3-chloromethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (mp 204-205°C (dec.)) was used in the next step without further treatment. A small sample was recrystallized from EtOAc for NMR and CHN analysis.

^{1}H-NMR ($CDCl_3$) d 2.28 (s, 3H, 2-CH_3), 3.80 (s, 3H, CH_3N-), 3.89 (s, 3H, CH_3O-), 4.86 (s, 2H, CH_2Cl) and 5.62 (s, 1H, 6-*H*). Anal. C; 55.71, H; 5.41, N; 5.70, Cl; 14.00% Calc. $C_{12}H_{12}NO_3Cl.0.33H_2O$ C; 55.49, H; 4.88, N; 5.39, Cl; 13.68%

GENERAL METHOD FOR THE SYNTHESIS OF TARGET COMPOUNDS OF TYPE A.

5-Methoxy-3-hydroxymethyl-1,2-dimethylindole-4,7-dione (**52**, 500mg, 1.97mmol) was dissolved in CH_2Cl_2 (50mL) together with pyridine (5mL) and the appropriate carbonyl chloride (5mmol) added. The solution was the heated under reflux for the reaction time given below, cooled and EtOAc (150mL) added followed by HCl (aq., 0.1M, 150mL). The organic layer was separated and washed again with HCl (aq., 0.1M, 100mL), sat. NaCl (aq., 100mL), dried and evaporated *in vacuo*. The residue was purified on silica, eluting with the solvent specified below and recrystallized to give the target compound.

B : GENERAL METHOD FOR THE SYNTHESIS OF TARGET COMPOUNDS OF TYPE B AND TYPE C

3-Chloromethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (**67**, 100mg, 0.39mmol) was dissolved in EtOAc (20mL) and the appropriate alcohol, phenol or thiol (1mmol) added dropwise or in portions with stirring. Stirring was continued at room temperature for the

reaction times given below and then water (20mL) added. The organic layer was separated and washed with sat.$NaHCO_3$ (aq., 20mL) and sat. NaCl (aq., 20mL), dried and evaporated to dryness. The residue was purified on silica, eluting with the solvent specified below, and recrystallized to give the target compound.

Example 33: Preparation of 1,2-Dimethyl-5-methoxy-3-(2-nitrobenzoyloxy)-ethylindole-4,7-dione (68)

General method A was employed (reaction time 0.75h), and the product eluted on silica with EtOAc (Rf=0.65), and recrystallized from EtOAc to give an orange solid (68%) : mp 199-200°C; ^{1}H-NMR ($CDCl_3$) d 2.34 (s, 3H, 2-C*H*$_3$), 3.80 (s, 3H, C*H*$_3$N), 3.91 (s, 3H, C*H*$_3$O), 5.53 (s, 2H, C*H*$_2$OCOAr), 5.62 (s, 1H, 6-*H*), 7.50-8.07 (m, 4H, 4 x Ar-*H*). Anal.

Example 34: Preparation of 1,2-Dimethyl-3-(2-fluorobenzoyloxy)methyl-5-methoxyindole-4,7-dione (69).

General method A was employed (reaction time 1.5h), and the product eluted on silica with EtOAc (Rf=0.6), and recrystallized from EtOAc to give a yellow solid (83%): mp 166-168°C; ^{1}H-NMR ($CDCl_3$) d 2.35 (s, 3H, 2-C*H*$_3$), 3.81 (s, 3H, C*H*$_3$N), 3.90 (s, 3H, C*H*$_3$O), 5.51 (s, 2H, C*H*$_2$OCOAr), 5.63 (s, 1H, 6-*H*), 6.98-7.52 (m, 3H, 3 x Ar-*H*) and 7.83-8.00 (dd, 1H, *J*=9Hz and *J*=1.5Hz, Ar3-*H*). Anal. C; 62.83, H; 4.59, N; 3.76% Calc. ($C_{19}H_{16}NO_5F.0.33H_2O$) C; 62.81, H; 4.59, N; 3.86%

Example 35: Preparation of 1,2-Dimethyl-3-(4-fluorobenzoyloxy)methyl-5-methoxyindole-4,7-dione (70).

General method A was employed (reaction time 1.25h), and the product eluted on silica with EtOAc (Rf=0.65), and recrystallized from EtOAc to give a yellow solid (88%) : mp 209-210°C; ^{1}H-NMR ($CDCl_3$) d 2.35 (s, 3H, 2-C*H*$_3$), 3.81 (s, 3H, C*H*$_3$N), 3.91 (s, 3H, C*H*$_3$O), 5.49 (s, 2H, C*H*$_2$OCOAr), 5.63 (s, 1H, 6-*H*), 6.95-7.27 (dd, 2H, *J*=9Hz and *J*=1Hz, Ar2,6-*H*) and 7.94-8.10 (dd, 2H, *J*=9Hz and *J*=1.5Hz, Ar3,5-*H*).
Anal. C; 63.34, H; 4.44, N; 3.88% Calc. ($C_{19}H_{16}NO_5F$) C; 63.86, H; 4.51, N; 3.92%.

Example 36: Preparation of 3-Benzoyloxymethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (71)

General method A was employed (reaction time 1.5h), and the product eluted on silica with EtOAc (Rf=0.75), and recrystallized from EtOAc/Me_2CO to give a yellow solid (69%) : mp 168-170°C; ^{1}H-NMR ($CDCl_3$) d 2.31 (s, 3H, 2-CH_3), 3.76 (s, 3H, CH_3N), 3.86 (s, 3H, CH_3O), 5.46 (s, 2H, CH_2OCOAr), 5.58 (s, 1H, 6-*H*), 7.34-7.41 (m, 3H, 3 x Ar*H*) and 7.93-8.01 (m, 2H, 2 x Ar-*H*).

Example 37: Preparation of 3-(2-Acetoxybenzoyloxy)-methyl-1,2-dimethyl-5-methoxyindole-4,7-dione (72).

General method A was employed (reaction time 1.5h), and the product eluted on silica with EtOAc (Rf=0.5), and recrystallized from EtOAc to give a yellow solid (90%): mp 159-161°C; ^{1}H-NMR ($CDCl_3$) d 2.27 (s, 3H, CH_3CO_2Ar), 2.31 (s, 3H, 2-CH_3), 3.81 (s, 3H, CH_3N), 3.90 (s, 3H, CH_3O), 5.47 (s, 2H, CH_2OCOAr), 5.63 (s, 1H, 6-*H*), 7.01-7.53 (m, 3H, 3 x Ar*H*) and 7.94-8.04 (dd, 1H, *J*=9Hz and *J*=1Hz, Ar-*H*).

Anal. C; 63.81, H; 4.81, N; 3.71% Calc. ($C_{21}H_{19}NO_7$) C; 63.47, H; 4.82, N; 3.52%

Example 38: Preparation of 3-Acetoxymethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (73)

General method A was employed (reaction time 0.5h), and the product eluted on silica with EtOAc (Rf=0.6), and recrystallized from EtOAc to give a yellow solid (90%): mp 185-186°C; ^{1}H-NMR ($CDCl_3$) d 2.04 (s, 3H, CH_3CO), 2.28 (s, 3H, 2-CH_3), 3.81 (s, 3H, CH_3N), 3.90 (s, 3H, CH_3O), 5.24 (s, 2H, CH_2OCOCH_3) and 5.62 (s, 1H, 6-*H*).

Example 39: reparation of 3-(Cyclohexylcarbonyloxy)-methyl-1,2-dimethyl-5-methoxyindole-4,7-dione (74).

General method A was employed (reaction time 0.25h), and the product eluted on silica with EtOAc (Rf=0.75), and recrystallized from EtOAc to give a yellow solid (65%) : mp 164-165°C; ^{1}H-NMR d 1.2-1.83 (m, 11H, 11 x cyclohexyl-*H*), 2.27 (s, 3H, 2-CH_3), 3.80 (s, 3H, CH_3N), 3.89 (s, 3H, CH_3O), 5.22 (s, 2H, CH_2OCOR) and 5.62 (s, 1H, 6-*H*).

Example 40: Preparation of 1,2-Dimethyl-3-(4-nitrophenoxy)-methyl-5-methoxyindole-4,7-dione (75).

General method B was employed (reaction time 0.5h), and the product eluted on silica with EtOAc/hexane (1:1, Rf=0.7), and recrystallized from EtOAc to give an orange solid (54%) : mp 215-216°C (dec.); ^{1}H-NMR d 2.33 (s, 3H, 2-C*H*$_3$), 3.81 (s, 3H, C*H*$_3$N), 3.89 (s, 3H, C*H*$_3$O), 4.99 (s, 2H, C*H*$_2$OAr), 5.62 (s, 1H, 6-*H*) and 6.79-6.93 (m, 4H, 4 x Ar-*H*).

Example 41: Preparation of 1,2-Dimethyl-3-(4-fluorophenoxy)-methyl-5-methoxyindole-4,7-dione (76).

General method B was employed, and the product eluted on silica with EtOAc/hexane (1:1, Rf=), and recrystallized from EtOAc to give an solid (40%).

Example 42: Preparation of 1,2-Dimethyl-3-(2-fluorophenoxy)-methyl-5-methoxyindole-4,7-dione (77).

General method B was employed, and the product eluted on silica with EtOAc/hexane (1:1, Rf=), and recrystallized from EtOAc to give an solid (55%).

Example 43: Preparation of 3-(2-Carbomethoxythiophenyl)-methyl-1,2-dimethyl-5-methoxyindole-4,7-dione (78).

General method B was employed (reaction time 2h), and the product eluted on silica with EtOAc/hexane (1:1, Rf=0.25), and recrystallized from EtOAc to give an orange solid (66%) : mp 214-216°C ; ^{1}H-NMR ($CDCl_3$) d 2.21 (s, 3H, 2-C*H*$_3$), 3.77 (s, 3H, C*H*$_3$N), 3.86 (s, 6H, C*H*$_3$O and CO$_2$C*H*$_3$), 4.39 (s, 2H, C*H*$_2$SAr), 5.59 (s, 1H, 6-*H*), 7.28-7.49 (m, 3H, 3 x Ar*H*) and 7.95 (d, 1H, *J*=9Hz, Ar-*H*).

Example 44: Preparation of 3-Benzyloxymethyl-1,2-dimethyl-5-methoxyindole-4,7-dione (79).

General method B was employed (reaction time 1h) but with the addition of K_2CO_3 (138mg, 1mmol) to the reaction mixture, and the product eluted on silica with

EtOAc/hexane (1:1, Rf=0.6), and recrystallized from EtOAc to give an orange solid (53%): mp 132-133°C (dec.); ^{1}H-NMR ($CDCl_3$) d 2.25 (s, 3H, 2-CH_3), 3.80 (s, 3H, CH_3N), 3.86 (s, 3H, CH_3O), 4.59 (s, 2H, 3-CH_2OCH_2Ar), 4.74 (s, 2H, 3-CH_2OCH_2Ar), 5.60 (s, 1H, 6-*H*) and 7.28-7.36 (m, 5H, 5 x Ar*H*). Anal. C; 67.81, H; 5.95, N; 4.49% Calc. ($C_{19}H_{19}NO_4.0.5H_2O$) C; 68.26, H; 5.99, N; 4.19%

Example 45: Preparation of 3-Benzoyloxymethyl-2-cyclopropyl-5-methoxy-1-methylindole-4,7-dione (80); 2-cyclopropane derivative.

General method A was employed (reaction time 1.5h) using compound **20**, and the product eluted on silica with EtOAc/hexane (1:1, Rf=0.35), and recrystallized from EtOAc/Me_2CO to give a yellow solid (68%): mp 221-223°C; ^{1}H-NMR ($CDCl_3$) d 0.65-0.82 (m, 2H, cyclopropyl-CH_2), 1.11-1.23 (m, 2H, cyclopropyl-CH_2), 1.61-1.71 (m, 1H, cyclopropyl-*H*), 3.79 (s, 3H, CH_3N), 4.03 (s, 3H, CH_3O), 5.56 (s, 2H, CH_2OCOAr), 5.64 (s, 1H, 6-*H*), 7.31-7.49 (m, 3H, 3 x Ar*H*) and 7.96-8.08 (m, 2H, 2 x Ar-*H*). Anal. C; 69.04, H; 5.30, N; 3.82% Calc. ($C_{21}H_{19}NO_5$) C; 69.03, H; 5.24, N; 3.83%.

Example 46: 5-(2-Methylaziridin-1-yl)-3-(2-nitrobenzoyloxymethyl)-1,2-dimethylindole-4,7-dione (81).

Compound **3** (0.1g, mmol) was dissolved and stirred in freshly distilled 2-methylaziridine (3mL, ca.50mmol) for 2.5h. The solution was evaporated *in vacuo* and the residue redissolved in EtOAc, evaporated until a red precipitate appeared and the solid collected. The red solid was recrystallized from EtOAc to give **81** (85mg, %): mp 168-170°C; ^{1}H-NMR ($CDCl_3$) d 1.42 (d, 3H, J=4.5Hz, azir-CH_3), 2.01-2.15 (m, 3H, azir-$CHCH_2$), 2.33 (s, 3H, 2-CH_3), 3.90 (s, 3H, CH_3N-), 5.54 (s, 2H, CH_2OCOAr), 5.73 (s, 1H, 6-*H*), 7.53-8.01 (m, 4H, 4 x Ar-*H*).

Example 47: Preparation of 5-(2-Methylaziridin-1-yl)-3-benzoyloxymethyl-1,2-dimethylindole-4,7-dione (82).

This compound was prepared from **6** by the same method used for the synthesis of **82**. The red solid was recrystallized from EtOAc to give **17** (70 %): mp 133-134°C; ^{1}H-NMR ($CDCl_3$) d 1.42 (d, 3H, J=4.5Hz, azir-C*H*$_3$), 2.01-2.15 (m, 3H, azir-C*H*C*H*$_2$), 2.33 (s, 3H, 2-C*H*$_3$), 3.90 (s, 3H, C*H*$_3$N-), 5.54 (s, 2H, C*H*$_2$OCOAr), 5.73 (s, 1H, 6-*H*), 7.34-7.41 (m, 3H, 3 x Ar*H*) and 7.93-8.01 (m, 2H, 2 x Ar-*H*). Anal. C; 67.96, H; 5.67, N; 7.23%, Calc. ($C_{21}H_{20}N_2O_4.0.5H_2O$) C; 67.56, H; 5.63, N; 7.51%.

Example 48: Prepration of 1,2-Dimethyl-3-(4-methylpiperazin-1-yl)methyl-5-methoxyindole-4,7-dione (83).

General method B was employed (reaction time 1h) but using N-methylpiperazine (0.65mL, 0.58mmol) in place of the alcohol or thiol, and the product eluted on silica with MeOH (Rf=0.15) to give **83** as an orange solid (38%): mp 159-162°C (dec.); ^{1}H-NMR ($CDCl_3$) d 2.24 (s, 6H, 2-C*H*$_3$ and N-C*H*$_3$), 2.31-2.62 (m, 8H, 4 x piperazine-C*H*$_2$), 3.73 (s, 2H, 3-C*H*$_2$N), 3.79 (s, 3H, C*H*$_3$N), 3.88 (s, 3H, C*H*$_3$O) and 5.69 (s, 1H, 6-*H*).

Example 49: Preparation of 5-(Aziridin-1-yl)-1,2-dimethyl-3-(4-methylpiperazin-1-yl)methylindole-4,7-dione (84).

Compound **83** (50mg, 0.158mmol) was stirred for 0.3h with 1*H*-aziridine **(CAUTION!)** at room temperature. Excess aziridine was removed *in vacuo* and the residue twice redissolved in EtOAc (5mL) and evaporated to dryness. The residue was recrystallised from EtOAc to give **84** as a dark red solid (mg, 62%): mp 143-146°C (dec.); ^{1}H-NMR ($CDCl_3$) d 2.17 (s, 4H, aziridine), 2.25 (s, 6H, 2-C*H*$_3$ and N-C*H*$_3$), 2.31-2.62 (m, 8H, 4 x piperazine-C*H*$_2$), 3.74 (s, 2H, 3-C*H*$_2$N), 3.87 (s, 3H, C*H*$_3$N), and 5.73 (s, 1H, 6-*H*).

The amount of compound to be adminstered will of course vary with individual and cancer type. However, suitable doses will be typically within the range 1-200mg/kg bodyweight, preferably 10-150mg/kg and more preferably 30-100mg/kg.

The form of adminstration will also vary, with formulations suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular and intravenous injection) being useable. Formulations may range from pure drug and simple aqueous solutions thereof , eg. in water or saline, to those including solid and/or more complex components such as liquid or solid carriers, diluents and active agents. Particular forms available include *inter alia* capsules, cachets, tablets or lozenges, boluses, electuaries or pastes containing solid or liquid compound of the invention, or suspensions, syrups, emulsions etc in liquid form. Suitable formulations will occur to those skilled in the art of pharmacy and may be exemplified by those used for the current lead EO9 and the antimicrobial agents described previously.

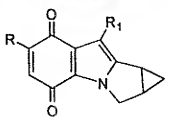
Simple saline injections may be used for the purpose of demonstrating efficacy of the compounds.

Biological Evaluation of Compounds 18 to 84 *In Vitro*

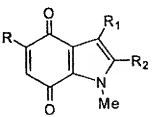
Example 50: MTT assay

Selective toxicity to hypoxic V79-379A cells was determined for all compounds using the MTT assay as has been described previously (see references 7 to 9). These results are presented in the Table 1 below, where C_{50} (air) values, the concentration required to kill 50% of the aerobic cells under the conditions of the assay, are divided by C_{50} (N_2) values, concentrations required to kill hypoxic cells, to give hypoxic cytotoxicity ratios (HCR), which enable quantitative comparisons of bioreductive activities of drugs.

TABLE 1 Compounds 1 to 66



A



B

	Type	R	R_1	R_2	C_{50}(Air) μM	$C_{50}(N_2)$ μM	HCR*
1	MMC	-	-	-	0.8[a]	0.4[a]	2.0[a]
2	A		CH_2OCONH_2	-	0.003[b]	0.003[b]	1.0[b]
3	EO9	-	-	-	0.19±0.027	0.0038±0.00057	50.3

4	A	MeO	CH_2OH	-	108.4±5.9	60.6±7.4	1.8
5	A		CH_2OH	-	0.965±0.11	0.073±0.011	13.2
18	B	MeO	CO_2Me		103.5±5.2	59.8±11.4	1.7
20	B	MeO	CH_2OH		540±52	820±83	0.65
23	B	MeO	CH_2OCO_2Ph		250±24	60±9.8	4.2
24	B	MeO	CH_2OCONH_2		29±5.6	0.44±0.023	65.9
19	B		CO_2Me		1.72±0.18	0.93±0.067	1.8
21	B		CH_2OH		0.603±0.099	0.0058±0.0013	103.5
25	B		CH_2OCONH_2		3.33±0.75	0.074±0.015	45.0
22	B		CH_2OH		130±9.8	5.6±0.6	23.4
26	B		CH_2OCONH_2		12.5±2.9	0.459±0.096	27.23
35	B	MeO	CO_2Me		150±15	150±15	1.0

36	B	MeO	CH_2OH		800±80	200±20	4.0
37	B		CH_2OH		25.7±3.0	0.79±0.14	32.5
38	B		CH_2OH		127.8±13.5	13.9±1.5	9.2
40	B	MeO	CH_2OCONH_2		20.9±1.67	0.117±0.018	178.6
41	B		CH_2OCONH_2		47.5±14.6	5.46±0.43	8.7
42	B		CH_2OCONH_2		20.6±2.5	0.87±0.215	23.7
43	B	MeO	Me		1.236±0.189	0.657±0.063	1.88
44	B		Me		0.333±0.014	0.188±0.011	1.77
45	B	MeO	CH_2OH	Cyclohexyl	122.4±17.5	20.5±5.3	6.0

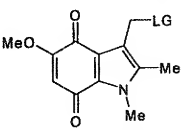
46	B		CH_2OH	Cyclohexyl	34.5±6.0	0.93±0.078	37.0
52	B	MeO	CH_2OH	Me	1077±44	284.8±37.6	3.78
53	B		CH_2OH	Me	0.149±0.011	0.0116±0.0008	12.8
54	B		CH_2OH	Me	94±7.6	0.5±0.07	188
55	B		CH_2OH	Me	202±11	14.2±1.7	14.2
56	B		CH_2OH	Me	1260±126	500±120	2.5
62	B	MeO	CH_2OH	H	220±20	240±23	0.92
63	B		CH_2OH	H	0.153±0.013	0.0086±0.0009	15.4
64	B		CH_2OH	H	4.42±1.17	0.0179±0.02	24.7
65	B	MeO	CH_2OCONH_2	H	3.1±0.24	0.037±0.007	83.8
66	B		CH_2OCONH_2	H	0.00019±0.000032	0.00013±0.000025	1.46

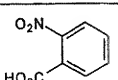
*HCR = hypoxic cytotoxicity ratio (C_{50}(Air)/C_{50}(N_2)).

[a] Stratford, I.J. *et al.*(1990), in Selective Activation of Drugs by Redox Processes; Adams, G.E. *et al.*, Eds., Plenum, N.Y.

[b] Moody, C.J. *et al.*(1994), Anti-Cancer Drugs, **5**, 367-372.

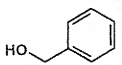
TABLE 2: LEAVING GROUP ACID DISSOCIATION CONSTANTS AND HCR (MTT) OF DRUGS WITH VARYING INDOLOQUINONE 3-METHYLENE LEAVING GROUPS



Compound	LG(H)	pKa (H^+)[1,2]	C_{50}Air	$C_{50}N_2$	HCR
RB94564J **67**	HCl	-2.2	-	-	-
RB96709J **68**		2.21	158.9 ±13.0	11.4 ±1.54	**14.0**

RB96716N 69		3.2	163.8 ±24.7	2.06 ±0.25	**79.5**
		3.42			
RB96715N 70		3.98	27.13 ±3.12	0.29 ±0.03	**93.5**
RB96708N 71		4.14	16.14 ±5.14	0.197 ±0.045	**82.0**
RB96714N 72		4.5	29.4 ±3.8	1.38 ±0.14	**21.3**
RB96717N 73	AcOH	4.75	27.3 1.54	2.45 ±0.18	**11.1**

RB96727N **74**		4.9[3]			
RB96713J **75**		7.15	72.9 ±19.3	1.15 ±0.136	**63.4**
RB96725N **78**		7.8[4]	319.6 ±91.8	369.1 ±77.1	**0.86**
RB96734N **77**		8.81	472.0 ±37.5	282.4 ±107.3	1.7
RB96728N **76**		9.81			

RB94547J					
50	H_2O	15.74	1077.0 ±44.0	284.8 ±37.6	**3.78**
RB96712J					
79		15.9[5]	225.1 ±14.6	412.0 ±31.8	**0.55**

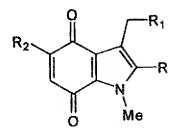
1. Streitwieser, A.; Heathcock, C. H. In *Introduction to Organic Chemistry*, Macmillan Pub. Co., Inc., New York, 1981.

2. Weast, R.C.; Astle, M. J. In *Handbook of Chemistry and Physics* (62nd edn.) 1981-82.

3, 4, 5 Values for $C_2H_5CO_2H$, C_6H_5SH and C_2H_5OH from ref.1.

Other compounds prepared include those where the leaving group is 2,4,6 trichloro phenol and 4-dimethylamino benzoac acid having pKa (H^+) of 6.0 and 4.92 respectively.

TABLE 3:DATA AVAILABLE ON COMPOUNDS 80-84



Compound	R	R_1	R_2	C_{50}Air	$C_{50}N_2$	HCR
80	cyclopropyl	benzoyloxy	MeO	197±68.9	1.01±0.07	196
81	methyl	2-nitrobenzoyloxy	2-methylaziridin-1-yl	36.2±2.7	1.05±0.15	34.5
82	methyl	benzoyloxy	2-methylaziridin-1-yl	1.22±0.16	0.062±0.0071	19.7
84	methyl	4-methylpiperazin-1-yl	aziridin-1-yl	11.01±1.12	0.025±0.0026	440

Example 52: Effect of compounds on RIF-1 and KHT tumour cells when administered with single dose radiation regimen.

Compounds 21 and 54 (RB 94573 and RB 94577) were applied to RIF-1 and KHT tumour cells in separate experiments with presence and absence of single doses of radiation (15GY and 10 GY respectively for 21 and 54). Maximum tolerated doses and tumour response experiments were carried out as described in reference 9. Tumour bearing mice were given doses of radiation chosen to kill most of the oxic cells in the tumours with the measured response reflecting the survival of residual hypoxic clonogenic cells (see reference 10). Indoquinones were given immediately after X-rays such that any therapeutic response greater than that achieved by radiation alone is a reflection of residual hypoxic cell killing. These conditions were achieved by giving 10GY to KHT tumours and 25 GY to RIF-1 tumours. Each experiment also included mice exposed to radiation without drug and with drug alone.

Results are shown in Figures 6 to 9. It can be seen that while the results are additive in the case of the KHT cells, providing destruction of tumour cells down to a surviving fraction of as low as less than 10^{-4}, the RIF-1 cells show a synergistic effect with surviving fraction being less than 10^{-6}.

Example 53: Effect of compound 54 (RB 94577) with fractionated dose radiation regimen.

Four daily doses of 2.5 Gy of X-rays were administered to RIF-1 cells followed immediately by 20mg/Kg of compound 52 after each fraction. Results are given in the Table 4 below.

TABLE 4 RB94577 (54) + X-rays in fractionated treatments

4 daily doses of 2.5 Gy X-rays followed immediately by 20 mg/kg RB94577 after each fraction. Tumours were excised 24 hours after last dose of drug to assay cell survival.

Treatment	Relative surviving fraction
Control	1.0
4 x 20 mg/kg RB94577	0.13
4 x 2.5 Gy	3.3 x 10-2
RB94577 + X-rays	1.6×10^{-3}

TABLE 5

Effect of fractionated treatments with RB94577 (54) and radiation on RIF-1 tumours.

Treatment	Relative Surviving Fraction
Control-No compound or radiation	4x 20mg/kg/day
4x 30 mg/kg/day	4x 40 mg/kg/day
1.00	0.13
1.3x 10-2	$0.9x\ 10^{-3}$

TABLE 6

Interaction between RB94577 (54) and cisPlatin in RIF tumour-no-radiation.

Treatment	Relative Surviving Fraction
50 mg/kg Compound 54 alone	0.1
3 mg/kg cisPlatin alone	$5x\ 10^{-2}$
Compound 54+cisPlatin (5min*)	$4.6x\ 10^{-4}$
Compound 54+cisPlatin (60min*)	$3.3x\ 10^{-4}$
cisPlatin+Compound 54 (60min*)	$7.9x\ 10^{-4}$

*The time between adminstration of the first mention agent and the second is indiated in minutes. Effect of the compound of the invention and cisPlatin is greater than additive in this assay.

TABLE 7:

Compound 53 as compared to EO9.

Cell line	Origin	DTDActivity	EO9IC_{50}	Cmpd53IC_{50}
A549	NSCLC	4980	7	6.2
322	NSCLC	4510	15	79.7
HT29	Colon	2750	157	82.3
522	NSCLC	550	32	17.5
841	SCLC	440	51	16.4
417	SCLC	116	210	155
MDA468	Breast	63	1720	3648
T47D	Breast	39	5110	1826
MDA231	Breast	8	285	1041
249	SCLC	2.5	3710	1804

DTD= DT diaphorase activity in nmol cytochrome c reduced per min per mg protein

IC_{50} (nM) concentration required to kill 50% of cells following four days incubation of cells with drug in air.

Table 8 IC_{50} (μm) for various quinones on various cell lines.

Compound	MDA231			MDA468			A549			HT29			SCCVII			V79		
	Air	N_2	HCR	Air	N_2	HCR	Air	N_2	HCR	Air	N_2	HCR	Air	N_2	HCR	Air	N_2	HCR
RB94573	2	0.5	4	-	-	-	0.02	0.02	1.0	-	-	-	-	-	-	0.6	0.006	100
RB94577	40	10	4	-	-	-	-	-	-	-	-	-	0.1	0.01	10	94	0.5	190
RB94582*	1.5	0.5	3	0.8	0.02	4	1.0	1.0	1.0	-	-	-	5	0.3	17	30	0.4	75
RB95662**	4.1	0.3	14	14	-	-	0.7	0.13	5.0	3.4	0.8	4.0	1.9	0.03	70	11	0.025	440

* Compound 24
**Compound 84

TABLE 9

Comparative tumour toxicities (relative surviving fraction) of compounds 21 and 54.

Tumour	RB95477-Compound 54	RB94573-Compound 21
KHT	1.2×10^{-1}	3.6×10^{-2}
RIF	1.5×10^{-2}	8.6×10^{-2}
SCCVII	2.3×10^{-2}	5.6×10^{-3}

Both drugs were given at 90 mg/kg ip and tumours were excised at 24 hours.

TABLE 10

Effects of Compound 54 as compared to EO9 of US 5097257.

Tumour	Diaphorase*	Control	4x vol-Cd 54	4xvol-EO9
H249	44	11.4	15.9	22.0
HT29	1544	11.4	19.5	17.4
H647	1960	12.2	13.5	21.1

*Activity in nmol cytochrome c reduced per min per mg protein

Compound 54 was given at 30 mg/kg i.p. while EO9 was given at 5 mg/kg. The maximum tolerated dose of Compound 54 is about 100 mg.kg while the max tolerated dose of EO9 is 5 mg/kg. H249 is human small cell cancer type; HT29 is human colon cancer type and H647 is human non-small cell lung cancer type.

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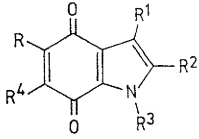
CLAIMS

1. Use of a compound of general formula I



or salt thereof

wherein

R and R^4 are independently selected from hydrogen, halogen and C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl, C_{1-6} alkoxy, phenoxy, C_{1-6} alkylthio, phenylthio, primary and secondary amino or hydroxy groups and

R^3 is hydrogen, hydroxy, a C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy or haloalkoxy group for the manufacture of a medicament for the treatment of neoplasms

characterised in that

R^1 is selected from a C_{1-6} alkyl or haloalkyl group, $-CO_2R^5$ where R^5 is hydrogen or a C_{1-6} alkyl or haloalkyl group, or a group $-CH_2-X$ where X is selected from groups of formula $-S-R^6$, $-O-R^6$ and $-N<^{R7}_{R8}$ where R^6 is a hydrogen or a leaving group the acid HR6 of which has a pKa of 10 or less and R^7 and R8 are the same or different and are selected from C_{1-6} alkyl or haloalkyl or together with the interjacent nitrogen form a heterocyclic ring of 5 to 7 atoms optionally substituted by C_{1-4} alkyl or haloalkyl and

R^2 is selected from hydrogen, C_{1-4} alkyl and haloalkyl or groups $-(CH_2)_nCHR^9R^{10}$ of more than four carbon atoms where n is an integer of 0 to 2 and R^9 and R^{10} are independently selected from a C_{1-4} alkyl or haloalkyl group, or R^9 and R^{10} together with the interjacent carbon atom form a C_{3-7} cycloalkyl or cycloalkenyl ring optionally substituted with one or more C_{1-4} alkyl or haloalkyl, or C_{2-4} alkenyl or haloalkenyl

groups.

2. Use of a compound as claimed in Claim 1 characterised in that R^1 is a group $-CH_2X$ where X is $-N<^{R^7}_{R^8}$ wherein R^7 and R^8, together with the interjacent nitrogen form a 5 to 7 membered heterocyclic ring containing nitrogen and carbon with optional oxygen or sulphur members.

3. Use of a compound as claimed in Claim 2 characterised in that the heterocyclic ring is a piperazinyl ring optionally substituted by one or more C_{1-4} alkyl or haloalkyl groups.

4. Use of a compound as claimed in Claim 3 wherein X is a 4-methylpiperazin-1-yl group.

5. Use of a compound as claimed in Claim 1 characterised in that R is selected from C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{2-4} alkenoxy, C_{2-4} haloalkenoxy and aziridin-1-yl optionally substituted with C_{1-4} alkyl, or C_{1-4} haloalkyl or C_{2-4} alkenyl or C_{2-4} haloalkenyl;
R^1 is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxycarbonyl, C_{1-4} haloalkoxycarbonyl and C_{1-4} alkyl substituted with an alkoxy, aryloxycarbonyloxy, aryloxycarbonyloxy or carbamoyloyloxy group;
R^2 is selected from $-(CH_2)_nCHR^9R^{10}$ where n is an integer from 0 to 2, and R^9 and R^{10} are independently selected from C_{1-4} alkyl and C_{1-4} haloalkyl or together with the interjacent carbon atom form a C_{3-6} cycloalkyl or cycloalkenyl group optionally substituted with C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl or C_{2-4} haloalkenyl;
R^3 is selected from C_{1-4} alkyl or haloalkyl and C_{2-4} alkenyl or haloalkenyl;
and R^4 is selected from hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl and C_{2-4} haloalkenyl.

6. Use of a compound as claimed in any one of Claims 1 to 5 characterised in that R is C_{1-4} alkoxy or is aziridin-1-yl optionally substituted with C_{1-4} alkyl or C_{1-4} haloalkyl.

7. Use of a compound as claimed in any one of the preceding claims characterised in that R^1 is a group $-CH_2-O-R^6$ or $-CH_2-S-R^6$ and R^6 is hydrogen or a group $-C(O)-R^{11}$ or $-R^{11}$ where R^{11} is an optionally substituted phenyl, benzyl or amino group.

8. Use of a compound as claimed in Claim 5 characterised in that R^1 is hydroxymethyl or a carbamate or aromatic acyl ester thereof.

9. Use of a compound as claimed in Claim 1 characterised in that R^2 is a C_{1-4} n-, iso- or cyclo-alkyl group.

10. Use of a compound as claimed in Claim 5 characterised in that R^2 is a methyl or cyclopropyl group.

11. Use of a compound as claimed in Claim 1 characterised in that R^3 is C_{1-4} alkyl.

12. Use of a compound as claimed in Claim 1 characterised in that R^4 is hydrogen.

13. Use of a compound as claimed in Claim 1 where R is aziridin-1-yl optionally substituted with C_{1-4} alkyl, R^1 is hydroxymethyl, R^2 is cyclopropyl or isopropyl or C_{1-4} n-alkyl, R^3 is methyl and R^4 is hydrogen.

14. Use of a compound as claimed in Claim 1 characterised in that the compound has a ratio of $C_{50}(Air)\mu M/C_{50}(N_2)\mu M$ of 40 or more.

15. Use of a compound as claimed in Claim 14 characterised in that it has a ratio of

$C_{50}(Air)\mu M/C_{50}(N_2)\mu M$ of 100 or more.

16. Use of a compound specifically as exemplified and described herein as any one of compounds 18 to 84 .

17. Use of a compound as claimed in Claim 16 and as defined herein as compound 21, 22, 24, 25, 26, 37, 40, 42, 46, 53, 54, 55, 63, 64, 65, 68, 69, 70, 71, 72, 73, 75, 80, 81, 82, 83 or 84 of the Examples.

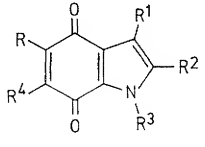
18. Use as claimed in any one of the preceding claims characterised in that the use is for the treatment of tumour cells.

19. Use as claimed in any one of the preceding claims characterised in that the use is for the treatment of cancer cells.

20. Use as claimed in any one of the preceding claims characterised in that the use is provided together with radiation treatment as a therapeutic.

21. Use as claimed in any one of the preceding claims characterised in that the use provides selective cytotoxicity to anoxic tumour cells.

22. A compound of general formula Ia



or a salt thereof characterised in that

R is C_{1-4} alkoxy or aziridin-1-yl optionally substituted with one or more C_{1-4} alkyl or

haloalkyl groups,

R^3 is hydrogen, hydroxy, C_{1-6} alkyl orhaloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy or haloalkoxy

R^4 is hydrogen or a C_{1-4} alkyl or haloalkyl group,

R^5 is hydrogen, C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl or C_{1-6} alkoxy,

R^1 is $-CO_2R^5$ where R^5 is hydrogen or a C_{1-6} alkyl or haloalkyl group, or is a group $-CH_2-X$ where X is selected from groups of formula $-SR^6$, $-O-R^6$ and $-N(R^7)(R^8)$ where R^6 is hydrogen or a leaving group the acid HR^6 of which has a pKa of 10 or less and R^7 and R^8 are the same or different and are selected from C_{1-6} alkyl or together with the interjacent nitrogen form a heterocyclic ring of 5 to 7 atoms optionally substituted by a C_{1-4} alkyl group and

R^2 is hydrogen or a C_{1-4} alkyl group or a group $-(CH_2)_nCHR^9R^{10}$ of more than four carbons where n is an integer of 0 to 2 and R^9 and R^{10} are independently selected from C_{1-4} alkyl and haloalkyl or R^9 and R^{10} together with the interjacent carbon atom form a C_{3-7} cycloalkyl or cycloalkenyl ring optionally substituted with one or more C_{1-4} alkyl or haloalkyl or C_{2-4} alkenyl or haloalkenyl groups,

with the provisos that

(i) when R is methoxy, R^1 is hydroxymethyl or a carbamate or C_{1-6} aliphatic acyl ester thereof, R^4 is methyl or ethyl and R^3 is methyl, optionally 2-substituted ethyl, or propyl or butyl then R^2 is not hydrogen, methyl, fluoromethyl, chloromethyl or ethyl,

(ii) when R is methoxy, R^4 is hydrogen, R^1 is hydroxymethyl or the propylcarbamate thereof and R^3 is ethyl then R^2 is not methyl,

(iii) when R is methoxy, R^2 is methyl, R^3 is ethyl and R^4 is methyl, R^1 is not a hydroxymethyl cyclohexylcarboxylate, benzoate, furamyl-2-carboxylate, 3-(2-dimethylaminoethyl)-piperazine-1-carboxylate, morphalino carbamate, 4-(3-hydroxypropyl)-piperazine carbamate, 4-(3-dimethylaminopropyl)-piperazine carbamate, and

(iv) when R is aziridino or ethoxy, R^1 is hydroxymethyl or a carbamate or C_{1-6} aliphatic acyl ester thereof; R^4 is methyl or bromo and R^3 is ethyl, R^2 is not methyl.

23. A compound as claimed in Claim 22 characterised in that R^1 is hydroxymethyl or a group $-CH_2-X$.

24. A compound as claimed in Claim 22 or 23 characterised in that R is aziridin-1-yl or 2-methylaziridin-1-yl.

25. A compound as claimed in Claim 22, 23 or 24 characterised in that R^3 is C_{1-4} alkyl or haloalkyl.

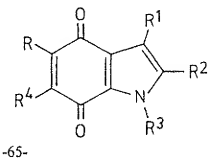
26. A compound as claimed in Claim 22, 23, 24 or 25 characterised in that R^2 is n-C_{1-4} alkyl, isopropyl, or C_{3-7} cycloalkyl.

27. A compound as claimed in claim 22 and as described herein as one of compound numbers 21, 22, 24, 25, 26, 37, 40, 46, 53, 54, 55, 63, 64, 65, 68, 69, 70, 71, 72, 73, 75, 80, 81, 82 or 84.

28. A process for preparing an optionally substituted aziridin-1-yl compound of formula II as described herein wherein R^1 is alkoxycarbonyl characterised in that it comprises reacting a corresponding 2-substituted -3-alkoxycarbonyl-5-alkoxy-1-alkylindole-4,7-dione compound with an optionally substituted aziridine.

29. A process for preparing a compound of formula Ia as described herein wherein R^1 is a hydroxymethyl group characterised in that it comprises reacting a corresponding 2-substituted-3-alkoxy-1-alkylindole-4,7-dione with an oxidising reagent and then reducing the resultant hydroquinone.

30. A compound of general formula II



characterised in that R is C_{1-4} alkoxy, R^1 is C_{1-4} alkoxycarbonyl and R^2, R^3 and R^4 are as described in any one of claims 22 to 26.

31. A method of treating a human or animal body for the purposes of preventing growth of, and/or killing, neoplasm cells comprising administering a compound or pharmaceutically acceptable salt thereof as claimed for use in any one of claims 1 to 21 or as claimed *per se* in any one of claims 22 to 26 to the body in a dose sufficient to prevent growth of or kill some or all of the neoplasm cells.

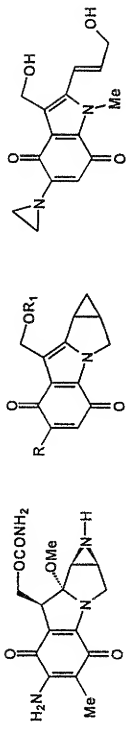
32. A method as claimed in claim 31 wherein the cells are tumour cells and/or cancer cells.

33. A method as claimed in claim 32 wherein the cells are hypoxic and/or anoxic cancer cells.

34. A method as claimed in any one of claims 31 to 33 comprising administering the compound or salt to the body within a set period of treatment of the body with doses of radiation, the doses of radiation being sufficient to prevent growth of or kill some or all of the cells supplied with blood.

35. A method as claimed in any one of claims 31 to 34 wherein the compound and radiation are adminstered within 1 to 30 days of each other.

36. A method as claimed in claim 35 wherein they are adminstered on the same day or within 7 days of each other.



1

2 (R=N◁, R1=CONH2)

3

4 (R= OMe, R1=H)

5 (R= N◁, R1=H)

Fig. 1

22

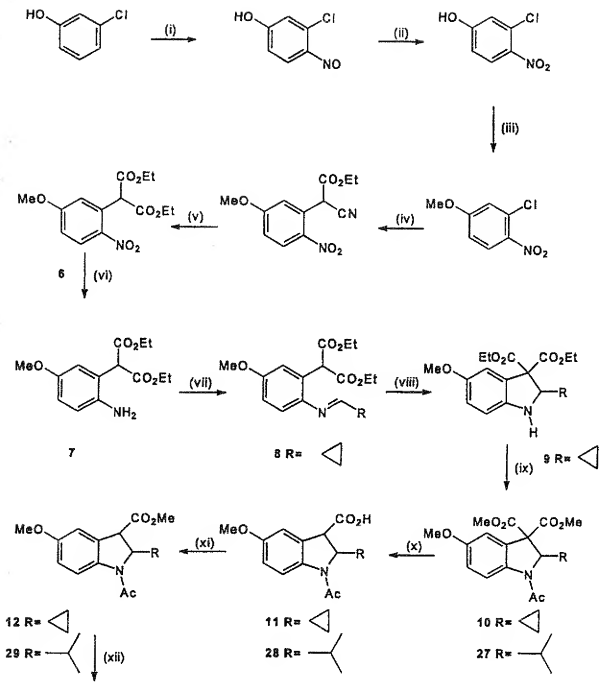
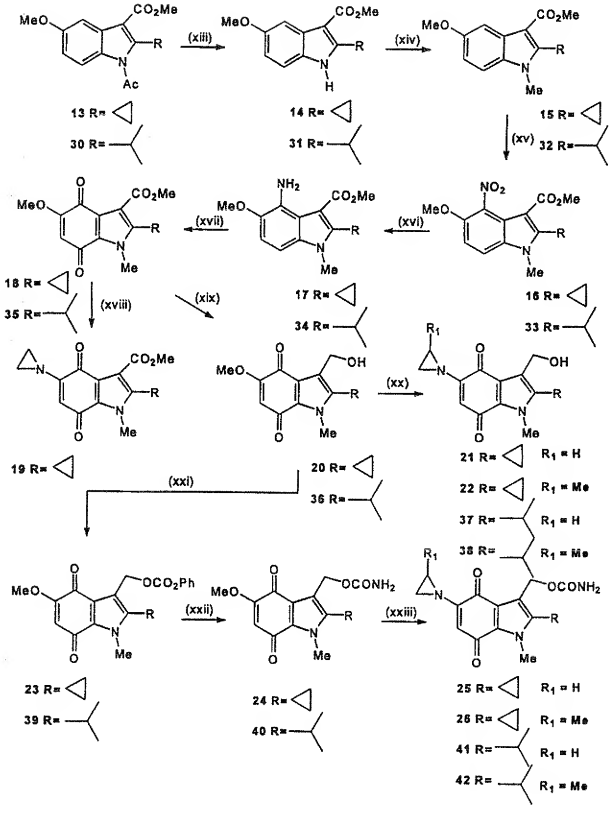

HO
Cl
(i)
NO
(ii)
NO2
(iii)
MeO
CO2Et
CN
(iv)
(v)
6
(vi)
NH2
7
(vii)
8 R=
(viii)
EtO2C
9 R=
(ix)
MeO2C
CO2Me
10 R=
27 R=
(x)
CO2H
11 R=
28 R=
(xi)
12 R=
29 R=
(xii)
Ac
N
H
R

Fig. 2


MeO
CO2Me
R
N
Ac
(xiii)
H
(xiv)
Me
13 R=
14 R=
15 R=
30 R=
31 R=
32 R=
(xv)
(xvi)
NO2
NH2
(xvii)
16 R=
17 R=
18 R=
33 R=
34 R=
35 R=
(xviii)
(xix)
O
OH
(xx)
19 R=
20 R=
21 R= R1 = H
22 R= R1 = Me
36 R=
37 R= R1 = H
38 R= R1 = Me
(xxi)
OCO2Ph
(xxii)
OCONH2
(xxiii)
23 R=
24 R=
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26 R= R1 = Me
39 R=
40 R=
41 R= R1 = H
42 R= R1 = Me

Fig. 3

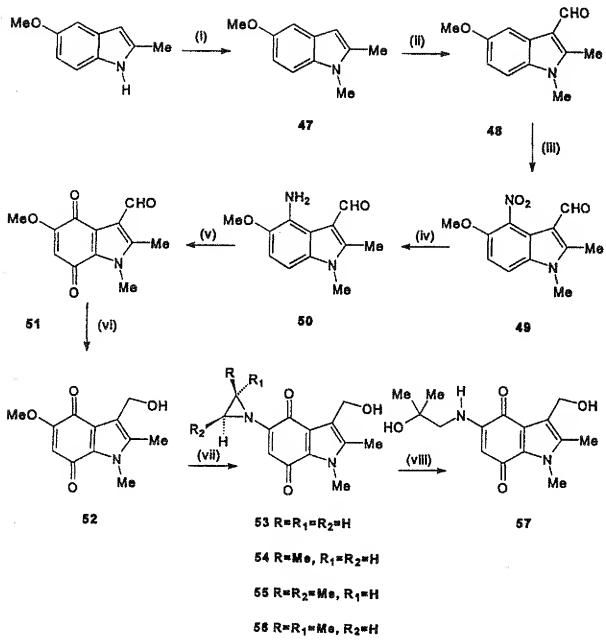
MeO
Me
N
H
(i)
N
Me
47
(ii)
CHO
48
(iii)
NO2
49
(iv)
NH2
50
(v)
51
(vi)
OH
52
R
R1
R2
(vii)
53 R=R1=R2=H
54 R=Me, R1=R2=H
55 R=R2=Me, R1=H
56 R=R1=Me, R2=H
(viii)
57

Fig. 4

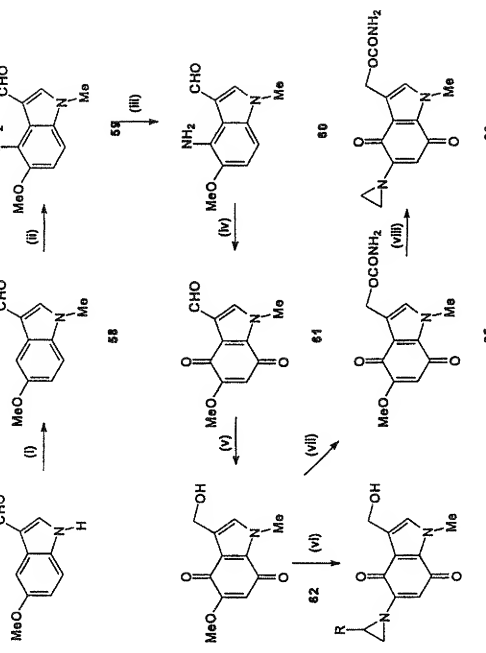
CHO
MeO
N
Me
H
58
(i)
(ii)
NO2
59
(iii)
NH2
60
(iv)
O
61
(v)
(vii)
OH
62
(vi)
R
63 R=H
64 R=Me
OCONH2
65
(viii)
66

Fig.5

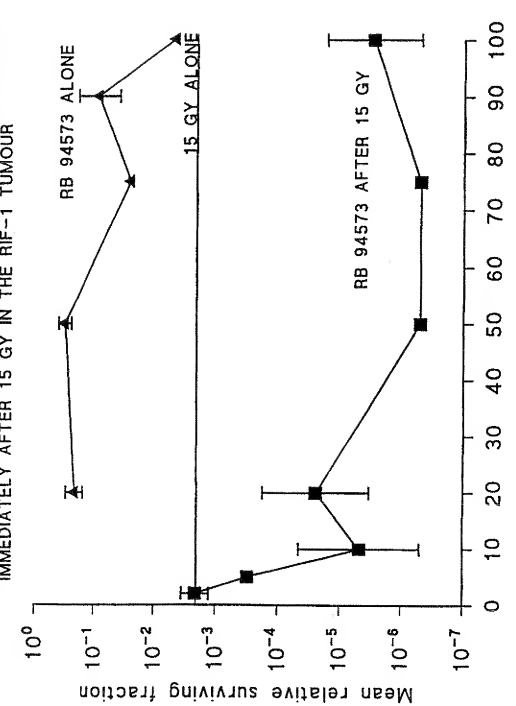
MEAN RELATIVE SURVIVING FRACTION AGAINST DOSE OF RB94573 ADMINISTERED IMMEDIATELY AFTER 15 GY IN THE RIF-1 TUMOUR
Mean relative surviving fraction
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
RB 94573 ALONE
15 GY ALONE
RB 94573 AFTER 15 GY
0 10 20 30 40 50 60 70 80 90 100
Dose of RB94573 (mg\kg)

Fig. 6

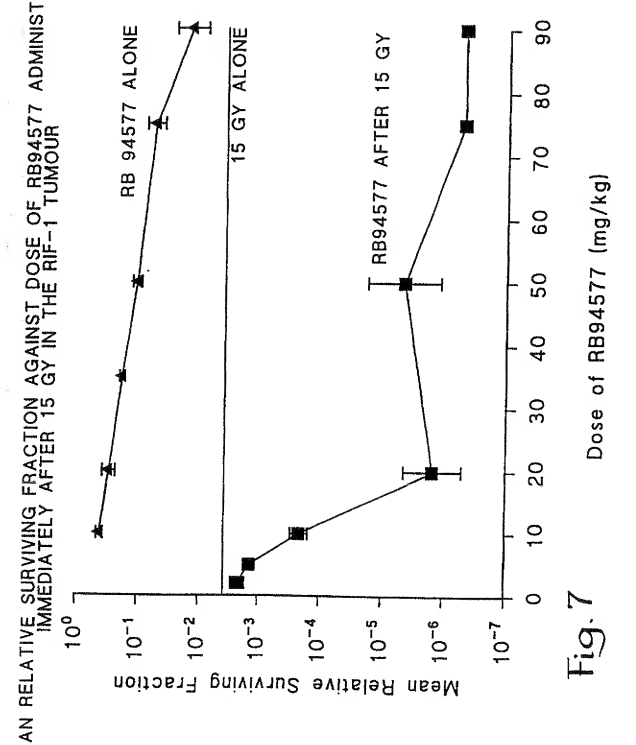
MEAN RELATIVE SURVIVING FRACTION AGAINST DOSE OF RB94577 ADMINISTERED IMMEDIATELY AFTER 15 GY IN THE RIF-1 TUMOUR
Mean Relative Surviving Fraction
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
RB 94577 ALONE
15 GY ALONE
RB94577 AFTER 15 GY
0
10
20
30
40
50
60
70
80
90
Dose of RB94577 (mg/kg)

Fig. 7

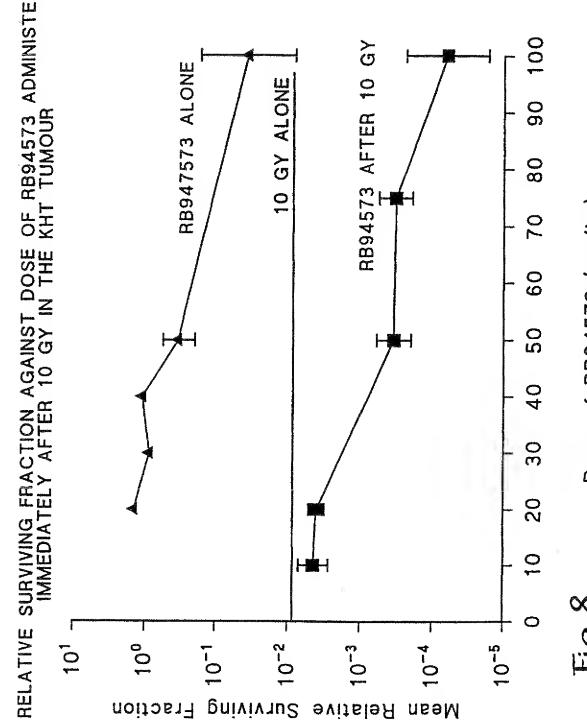
MEAN RELATIVE SURVIVING FRACTION AGAINST DOSE OF RB94573 ADMINISTERED IMMEDIATELY AFTER 10 GY IN THE KHT TUMOUR
Mean Relative Surviving Fraction
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
RB947573 ALONE
10 GY ALONE
RB94573 AFTER 10 GY
0 10 20 30 40 50 60 70 80 90 100
Dose of RB94573 (mg/kg)

Fig. 8

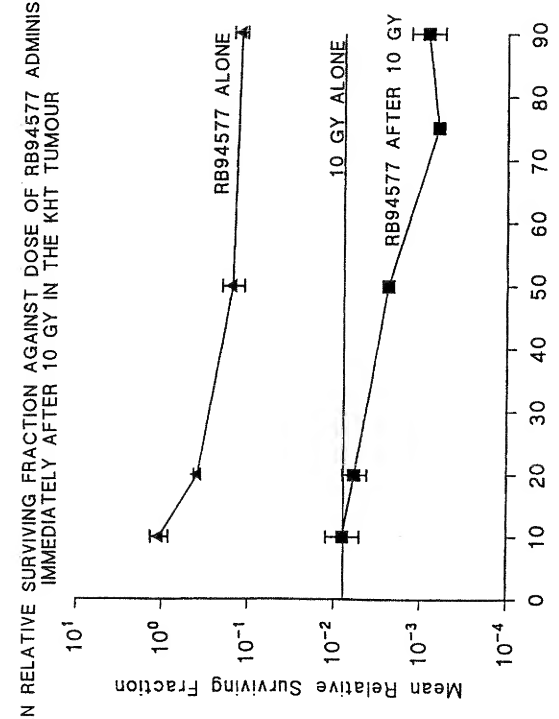
MEAN RELATIVE SURVIVING FRACTION AGAINST DOSE OF RB94577 ADMINISTERED IMMEDIATELY AFTER 10 GY IN THE KHT TUMOUR
Mean Relative Surviving Fraction
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
RB94577 ALONE
10 GY ALONE
RB94577 AFTER 10 GY
0 10 20 30 40 50 60 70 80 90
Dose of RB 94577 (mg\kg)

Fig. 9

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 96/03176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/42 A61K31/40 C07D209/12 C07D403/04
//(C07D403/04,209:00,203:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 22, 1994, pages 3834-3843, XP002027789 A.S. COTTERILL ET AL.: "Cyclopropamitosenes, Novel Bioreductive Anticancer Agents. Synthesis, Electrochemistry, and Biological Activity of 7-Substituted Cyclopropamitosenes and Related Indolequinones" cited in the application * See the whole document, in particular Table 4, p. 3837 * --- -/--	1-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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1

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 1997	17. 04. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Lauro, P

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INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/GB 96/03176

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 114, no. 7, 18 February 1991 Columbus, Ohio, US; abstract no. 61926a, page 672; XP002027842 see abstract & JP 02 225 461 A	1-30
X	THE JOURNAL OF ANTIBIOTICS, vol. 33, no. 8, 1980, pages 804-809, XP000651718 URAKAWA C; NAKANO K; IMAI R: "Synthesis and biological activities of 7-alkoxymitosanes" * See Table 1, compound no. 18 *	22
X	GB 1 087 325 A (AMERICAN CYANAMID) 18 October 1967 cited in the application see the whole document	22
Y	US 5 079 257 A (SPECKAMP ET AL.) 7 January 1992 cited in the application see column 3-4	1-30
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 8, 1989, pages 1866-1872, XP002027841 B.S. IYENGAR, W.A. REMERS, J.J. CATINO: "New 2-Substituted Indoloquinone Mitomycin Analogues" see the whole document	1-30

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information on patent family members

Inter nal Application No
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